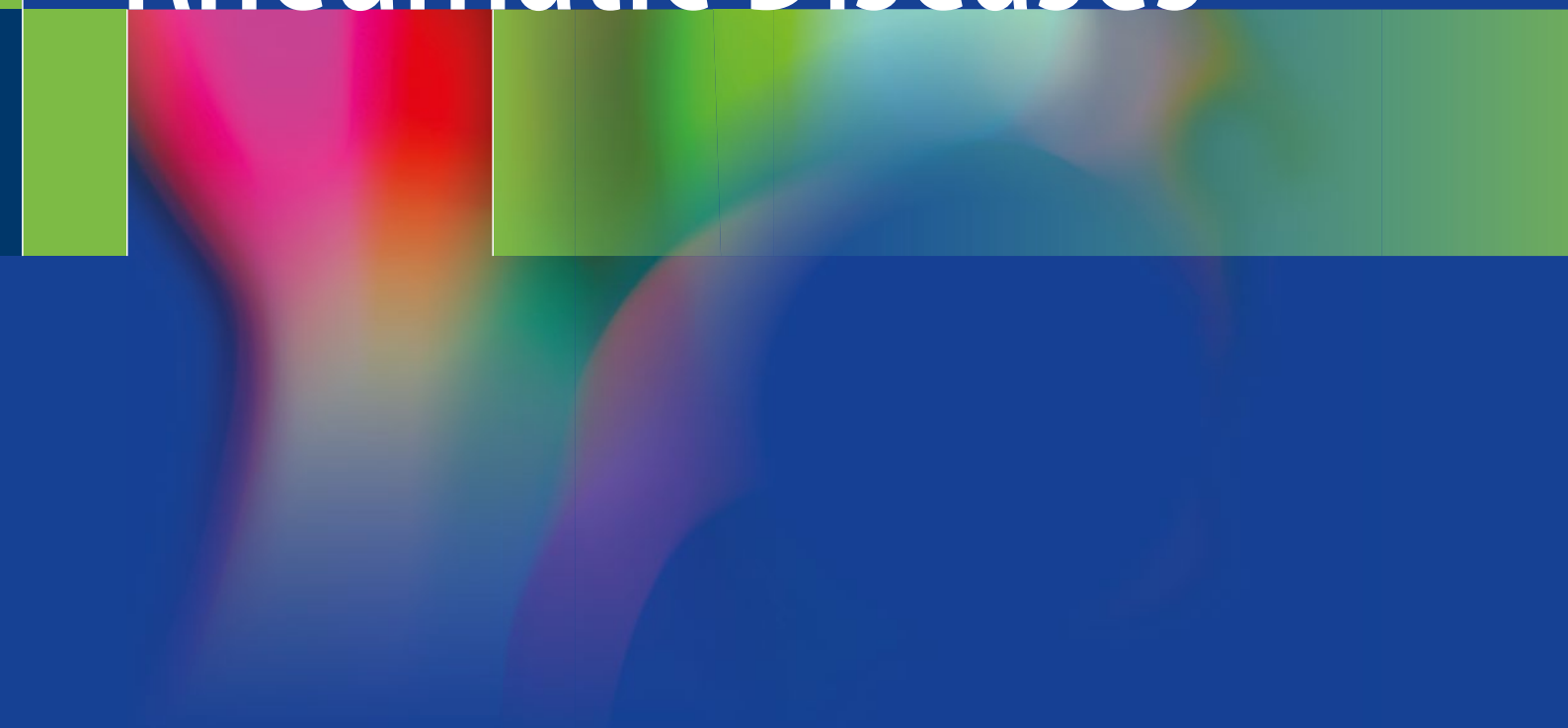
Luis R. Espinoza
Editor

Infections and the Rheumatic Diseases



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ISBN 978-3-030-23310-5 ISBN 978-3-030-23311-2 (eBook)
https://doi.org/10.1007/978-3-030-23311-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The intersection of infectious diseases and rheumatology has progressed at a torrid rate over the past generation; thus, it is timely to welcome such a comprehensive book as *Infections and the Rheumatic Diseases* for both the practitioner and for those engaged in basic and clinical investigations in this evolving field. Conceptually, the field can be viewed as a triptych painting, whereby in one frame infections are viewed as the etiology of rheumatic signs, symptoms, or as the cause of distinct nosological diseases (e.g., hepatitis C-associated cryoglobulinemia). Alternatively, in another frame, infections may represent formidable comorbidities to be dealt with by clinicians attempting to balance immunosuppressive regimens with a wide variety of chronic latent or persistent infections (e.g., hepatitis B or HIV). The final frame of this exhibit is the growing field of infections induced by our immune-based therapies which range from merely the frequent and mild ubiquitous respiratory infections observed to be increased in virtually every clinical trial of biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs) or the increasingly recognized rise in zoster infections associated with Janus kinase inhibitors. At the extreme, we as rheumatologists are increasingly linked to the induction of rare yet potentially life-threatening opportunistic infections with pathogens such as mycobacteria, endemic fungi, and viruses. Furthermore, we are now being challenged by how to handle the identification of new microbes and assess their relationship to clinical diseases which no longer simply follow Koch's postulates which served us well over the first century of the microbial era. New pathogens are rapidly being discovered due to advances in diagnostic technologies such as next-generation sequencing and culturomics (an evolving field developed to culture and identify unknown bacterial members of our microbiota as a part of the rebirth of culture techniques in microbiology). Such advances once considered clinically arcane now must be understood by the rheumatologic community.

Advances in the field of rheumatology and infectious disease also include new syndromes such as acute and chronic inflammatory arthritis secondary to the epidemiologically emerging alpha viruses now invading the western hemisphere (e.g., chikungunya). In addition, there is also a new and complex area emerging, whereby our technology has helped us define the footprints of ubiquitous pathogens such as EBV, CMV, and others, yet we have not etiologically clearly linked them to emerging disorders such as chronic fatigue syndrome and other maladies which remain medically unexplained.

The care of complex rheumatic diseases is now more of an interprofessional team sport than ever before. We in the field of rheumatology are constantly challenged to keep pace with numerous related fields of which infectious disease is increasingly prominent. What practitioner has not cared for patients where infections have not served as the etiology of a rheumatic disorder, or a comorbidity or complication of our therapies? The need for staying abreast of new infectious etiologies, new diagnostics, and new ways to assess prognosis and of course new therapies mandates close rheumatology and infectious disease collaboration for both care and investigation. I will close by sharing that the first combined fellowship program in rheumatology and infectious diseases was launched at the Cleveland Clinic in 2015 and has already

produced the first of what is hoped to be a growing fraternity of clinician investigators with board certification both in rheumatology and infectious diseases. The interest is strong and the future is bright for this new and emerging field.

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Preface

Infectious agents remain at the forefront of many maladies affecting mankind, despite the many advances in their therapeutic eradication. This has increasing relevance and importance when dealing with musculoskeletal disorders in which infections play an important role in causation, morbidity, and mortality. Old, newer, and emerging infectious disorders continue to affect populations worldwide, have a negative impact in public health, and also negatively impact the economy of afflicted countries.

The focus of this book is to highlight the relevance and importance of infectious agents in the etiology and pathogenesis of musculoskeletal disorders, as well as the role they play in affecting the natural course, disease expression, progression, and clinical response to conventional and biological therapy. There has been extraordinary development in biological therapies with the introduction of many types and classes of agents that possess excellent efficacy and safety. These agents are of particular importance to our topic because their use might be complicated by a variety of serious complications including opportunistic infections. An earlier version of this book was published over 30 years ago, and the editor of this work felt that the newer developments on this field merit an update.

The first section of the book discusses the role of bacterial infection. The opening chapter by Hudson and Carter discusses the role of the molecular biology of infectious agents in the genesis of inflammatory articular involvement. The potential role of ocular chlamydial infection and newer insights into chlamydial gene products into the pathogenesis of synovitis are discussed in depth. The next chapter by Attur and Scher provides an overview of microbiome and microbiota, which is a topic of great interest and relevance and is found to be a key element for hormonal, metabolic, and immunologic homeostasis for the host in health and disease states.

The next six chapters deal with the role of bacterial agents in the etiology, disease expression, clinical manifestations, and therapeutic management of common musculoskeletal disorders.

First, García-De La Torre and González-Bello present an update of gonococcal and non-gonococcal bacterial infection with emphasis on predisposing risk factors, clinical features, morbidity, and mortality and the use of newer agents in the management of septic arthritis. Septic arthritis in children is discussed further by Alarcón et al. The next two chapters by Tobón and Gotuzzo Herencia and Vega Villanueva, respectively, provide comprehensive reviews of specific infectious-related arthritides associated with *Salmonella* and *Brucella* infection, respectively. Next, Cohen-Rosenblum et al. provide an in-depth discussion of the etiology, clinical aspects, and management related to prosthetic septic arthritis. The last chapter in this section by Martín-Mola and Plasencia-Rodríguez provides an in-depth review of infection-related complications of the use of biologic agents in the therapy of rheumatic disorders.

The second section deals with the role of viruses in the etiology, disease manifestations, clinical complications, and therapeutic management of associated disorders. First, Reimold presents a comprehensive overview of the pathophysiology of viral disorders and vaccines. Viral and host predisposing factors that lend arthritogenic capacity to viruses and regulate viral growth and persistence such as genetic predisposition, innate and adaptive immune responses,

and host's comorbidities are discussed in detail. Perez-Alamino then presents an overview of the rheumatic manifestations associated with hepatitis B and C infection, as well as their therapeutic management recommendations. Vera-Lastra et al. next present an overview of chikungunya-associated arthritis. Chikungunya is a viral illness transmitted by the kind of mosquitoes that spread dengue and Zika virus. The most recent outbreak in the Caribbean and Americas is described. The next chapter focuses on arthritis associated with *Flavivirus* infections. Dr. Toloza and Agüero discuss emerging and re-emerging infections related to dengue and Zika. A comprehensive overview of the recent outbreaks is presented. Adizie and Adebajo next describe the inflammatory musculoskeletal manifestations associated with Ebola virus. Drs. Brom and Perandones describe the inflammatory musculoskeletal manifestations associated with parvovirus B19 infection. Characterization of its potential role in the pathogenesis of chronic arthritides and a comprehensive review of related literature are presented.

The next two chapters describe the clinical manifestations associated with retroviruses. First, Vega and Espinoza describe the inflammatory musculoskeletal clinical manifestations associated with HIV infection in the pre- and post-ART. Subsequently, Fuentes and Burgos provide a comprehensive overview of the clinical manifestations associated with HTLV-1 infection.

The final chapter in this section is devoted to rubella-related arthritis. Dr. Vega reviews clinical manifestations related to natural and vaccine-related inflammatory musculoskeletal manifestations.

The third section concerns with arthritis secondary to mycobacteria, fungi, and spirochetes. First, Oyoo and Genga describe the osteoarticular clinical manifestations associated with tuberculous and nontuberculous mycobacterial infections. This topic is of particular interest in view of its increased incidence associated with the use of biologic agents, especially in developing countries. Dr. Ribeiro et al. next discuss the clinical manifestations associated with leprosy as well as their therapeutic management. In addition, authors discussed newer insights on pathogenesis and autoimmune manifestations.

The next five chapters review musculoskeletal clinical manifestations associated with fungal disorders, some more prevalent than others, and with a geographic distribution. First, Dr. Echeverri presents an overview of coccidioidal arthritis, an endemic disorder in certain geographical areas of the world. Recent developments in epidemiology, diagnostic investigation, and therapeutic approaches are discussed. Histoplasmosis is discussed next. Dr. Pinto Peñaranda emphasizes the endemicity of this fungal infection and describes diagnostic pitfalls, as well as clinical and therapeutic considerations. Next, Dr. Restrepo-Escobar discusses another endemic disorder, blastomycosis arthritis, a prevalent disorder in northern United States and Canada. Its diagnosis, clinical manifestations, and therapy are discussed. *Candida* arthritis is reviewed by Drs. Alarcón and Bégué in a comprehensive manner including its epidemiology, clinical characterization, outcomes, and management. The final chapter on fungal-related arthritides is presented by Drs. Ramírez Gómez and Vélez Hoyos. They review a diverse group that includes *Aspergillus*, *Cryptococcus*, *Sporothrix schenckii*, paracoccidioidomycosis, and mucormycosis. Their diagnoses, clinical manifestations, and therapy are presented.

The chapter on syphilis-related musculoskeletal manifestations is discussed by Drs. Hajjaj-Hassouni and Rkain. This sexually transmitted infection remains relevant and important, in view of its increasing incidence among different populations. They present an overview of its epidemiology, clinical manifestations, and therapeutic management. Dr. Arzomand et al. next review another endemic disorder in the northeastern United States, Lyme disease, caused by *Borrelia burgdorferi*. Its pathogenesis, clinical stages, and therapy are well discussed.

Dr. Vega next discusses mycoplasma-related arthritis. These free-living microorganisms, primarily commensal residing on mucosal surfaces under certain conditions, may induce disease including arthritis in immunocompetent and immunosuppressed individuals. Its clinical characteristic, diagnosis, and therapeutic considerations are discussed.

Next, Dr. Márquez Hernández discusses parasitic-related rheumatic manifestations. This public health worldwide problem may at times involve the musculoskeletal system, and a high index of suspicion is necessary to arrive at proper and early diagnosis. Newest diagnostic techniques and more effective treatments are presented.

Finally, Drs. Cañete Crespillo and Ramírez García provide a comprehensive overview of Whipple disease, a rare infectious disease caused by *Tropheryma whipplei*. An excellent description of the localized and systemic forms of the disease is presented.

The next section of the book attempts to present a comprehensive review of the reactive arthritides in which genetic, immunologic, and environmental factors play a significant pathogenic role.

First, Drs. Naovarat and Reveille introduce the section reviewing the role that infectious microorganisms might play in the pathogenesis of spondyloarthritis. They provide an overview of potential mechanisms of action of a variety of microbial agents, especially gram-negative microorganisms. Newer insights are discussed in depth.

Rheumatic fever is presented next. This disorder is the prototype of reactive arthritis in which the host develops an immune response to streptococcal antigens. Newer insights into the pathogenesis, clinical manifestations, and therapy are discussed.

The pathophysiology of reactive is discussed next. Drs. Pathan and Inman described in depth newer insights into the pathogenesis of this disorder. Drs. Naovarat and Reveille next present an extensive description of the potential role of HLA-B∗27 and infection. This is followed by Dr. Espinoza's review of animal models of reactive arthritis. Development of animal models has facilitated a better understanding of the complex interaction between microbial agents, innate and adaptive immunity, and host responses. Drs. Carter and Hudson next present a comprehensive overview of the clinical manifestation and therapeutic strategies for reactive arthritis. Vasey and Espinoza next present an overview of the potential role of microbial agents in the pathogenesis of psoriatic arthritis. Lastly, Jatwani et al. discuss in depth the role of microbes in the pathogenesis of inflammatory bowel disease. They suggest that the use of new techniques focusing on molecular analysis of gut microflora in combination with genomic approaches is likely to further our understanding of the role that microorganisms play in the development of inflammatory disease.

The fifth and final section of the book discusses practical topics of great importance in the management of patients afflicted with rheumatic disorders. First, Jara et al. describe infections in patients with systemic lupus erythematosus, which, despite great advances in diagnosis and therapy, remain an important cause of morbidity and mortality.

The last two chapters of this book concern with vaccines in rheumatic diseases and climate change. First, Pineda et al. discuss the indications, contraindications, and efficacy of vaccines in patients with rheumatic disorders, as well as schemes to be used for patients traveling abroad. Lastly, Dr. Shellito presents an overview on the potential impact that climate change may have on the epidemiology of infectious diseases.

New Orleans, LA, USA Luis R. Espinoza, MD

Acknowledgment

This book is dedicated to the memory of John B. Zabriskie who was an inspiration to me in my formative years.

Special thanks go to the LSU Health Sciences faculty, especially the administration and Charles V. Sanders, Jr., Chairman of the Internal Medicine Department, who demonstrated resilience against the adversities caused by Hurricane Katrina and brought back our medical center to its present status.

I would also like to thank Luzlelia and Carmen Espinoza who provided me with guidance and support throughout the years.

My grateful thanks are also extended to Connie Walsh and Garth Haller, Springer, who provided significance assistance and encouragement for the completion of the book.

Finally, I extend my great appreciation to the many contributors without whose support, dedication, and work, this book could not have been possible.

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Part I

Basic Aspects of Bacterial Infections

The Molecular Biology of Chlamydiae as Exemplar of Bacterial Pathogenesis in the Rheumatic Diseases

1

John D. Carter and Alan P. Hudson

Introduction

Along with small pox, tuberculosis, trachoma, and several other clinical entities, the rheumatic diseases are among the oldest known afflictions of mankind. For just one example, some observations suggest that rheumatoid arthritis (RA) has existed in North America for 3000 years or more [1]. From historical times, skeletal remains of the Medici family from the late Renaissance were examined recently, and they demonstrated evidence for RA, uratic gout, and diffuse idiopathic skeletal hyperostosis [2]. William Harvey was originally diagnosed with "gout," but recent thinking suggests that his problem probably was erythromelalgia [3]. In the mid-nineteenth century, Herman Melville was afflicted severely by what today would be diagnosed as ankylosing spondylitis [4]. In the late nineteenth/early–mid-twentieth centuries, August Renoir, Alexey von Jawlensky, Raoul Dufy, and Niki de Saint Phalle all suffered from RA [5, 6]. James Joyce probably suffered from *Chlamydia*-induced reactive (inflammatory) arthritis [4].

Interestingly, and not terribly surprisingly, most of the ancient scourges of mankind were of infectious origin, and as developed in this volume, the rheumatic diseases are not exceptions. For one currently interesting example, RA was first described in what can be considered the modern clinical literature by Landre-Beauvais in 1800; the clinical designation "rheumatoid arthritis" was coined by Garrod in 1859 [7]. However, as mentioned, the disease itself is unquestionably far older than its official clinical description. Because of its high incidence and critical clinical consequences for patients, RA has, of course, been the subject of intensive research for many decades. Some studies from earlier in the twentieth century suggested an infectious origin for RA, with more recent reports indicating that the pathogenesis characteristic of the condition is of genetic origin. However, neither infection nor genetics nor any other single factor currently is accepted as causative in RA. We have suggested that the etiology of RA actually is complex and not simply assignable to either infection or genetics [8].

Detailed discussion of the pathogenic mechanisms inherent in the many arthritides resulting from various bacterial, viral, and fungal infections is developed in detail in the following chapters, but while the molecular genetic/molecular biological specifics of each differ, one general theme that emerges among all of them is the elicitation of inflammation, often severe, in joint tissues. This is especially the case for arthritides elicited by bacterial infections. We have studied the lower body arthritis elicited by prior genital infection with *Chlamydia trachomatis* for nearly 30 years, and more recently the similar clinical entity elicited by its close relative the respiratory pathogen *C. pneumoniae*. Those studies and the work of many others have demonstrated clearly that several unexpected and unusual aspects of the biology of these pathogens are critical to their ability to elicit and maintain arthritogenesis. Importantly as well, interactions between the host and pathogen contribute importantly to pathogenesis.

In this chapter, we outline the molecular genetic/molecular biologic details underlying the pathogenesis process elicited by chlamydiae in the human synovium. For reasons developed below, the arthritis elicited by these organisms can serve in many ways as exemplar for pathogenic details characteristic of bacterially induced arthritis in general. Clinical details, epidemiology, treatments, and other aspects of *Chlamydia*-induced arthritis are developed in Chap. 28. The chapters surrounding the latter present information regarding arthritides related to *Chlamydia*-induced arthritis but which result from other bacterial infections. Over the last several years, a few papers have appeared concerning clinical and epidemiologic aspects of *Chlamydia*-induced reactive arthritis

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_1

[e.g., 9–13], but it will be abundantly clear from what follows here that studies undertaken to elucidate the basic science underlying the pathogenesis characteristic of that clinical entity have been relatively scarce. For that reason, we provide several suggestions for areas of research that we consider important to support development of therapies to treat, and indeed to prevent, the arthritis.

Chlamydiae and *Chlamydia*-Induced Arthritis

Chlamydia trachomatis is an obligate intracellular bacterial pathogen that is the causative agent for important human diseases. In some regions of the world, well-defined strains (serovars) of the organism cause trachoma, which remains a significant cause of treatable blindness; other strains cause genital infections worldwide (for review see [14, 15]). In addition to these primary infections, it has been clear for many years that chlamydial infections frequently cause severe sequelae. These are foremost a function of genital infections with *C. trachomatis* and include fallopian tubule blockage leading to ectopic pregnancy, pelvic inflammatory disease, and other problems with the female upper reproductive tract. Importantly, another sequela is an inflammatory arthritis, which is the topic of this chapter and Chap. 28 (for review, see [14–19]). The arthritis is classified among the spondyloarthropathies, and it has been given several different clinical designations, including, originally, Reiter's disease [20]. Usually the arthritis has been referred to as reactive arthritis (ReA) and more recently simply as *Chlamydia*-induced arthritis [21].

Chlamydia pneumoniae is a respiratory pathogen first identified in 1986 and defined as a separate species a bit later [22, 23]. Infection with this organism apparently is common in all populations examined to date, and reinfection is frequent. Estimates indicate that pulmonary infections with the organism are responsible for perhaps half of all community-acquired pneumonia [23, 24]. Infections with *C. pneumoniae* also have been linked to severe sequelae, including asthmatic bronchitis, chronic obstructive pulmonary disease, atherogenesis, and an inflammatory arthritis similar to that elicited by genital infection with *C. trachomatis* (see [21, 25–27]). The clinical aspects of *C. pneumoniae*-induced arthritis mirror to some extent those characteristic of *C. trachomatis*-induced arthritis, although some differences are known.

The basic outline of chlamydial pathogenesis during primary infection of the genital tract has been defined through years of study. That process is a function of the biology of active infection by *C. trachomatis* – that is, it is a function of details attendant on the developmental cycle and later [28, 29]. The cycle is initiated by attachment of the extracellular form of the organism, the elementary body, to target host cells, upon which the organisms are taken into the host cell by an active process. The primary host cell type is epithelial, but other cell types can be infected as well [19, 30, 31]. The receptor to which chlamydiae attach on the host cell surface has been a target of research for decades, and a number of host surface molecules have been implicated (e.g., [32–34]). One report indicated that the receptor for *C. pneumoniae* attachment on endothelial cells is the lectin-like oxidized LDL receptor [35]. That observation is consistent with unpublished results from our group for attachment of either chlamydial species on epithelial cells [e.g., 36–39]). If these data are confirmed, it would provide some explanation for as yet unexplained aspects of chlamydial infection, such as how these organisms elicit phagocytosis in nonphagocytic cells. Once in the host cell cytoplasm, the organisms reside within a membrane-bound vesicle for the duration of their intracellular tenure. Within the inclusion, each elementary body undergoes a transcriptionally determined "differentiation" process that produces the vegetative growth form of the organism, the reticulate body. Each of these latter undergoes seven to eight cell divisions. Near the end of the cell division process for *C. trachomatis*, 80% or so of reticulate bodies dedifferentiate back to the elementary body form, and at about 48 h post-infection, those new extracellular forms are released to the external milieu by host cell lysis or exocytosis (for detailed review, see [19, 28, 39]). For *C. pneumoniae*, the cycle requires approximately 72 h for completion.

Studies from many groups have illuminated the means by which invading chlamydiae influence the host cell and its biochemical processes during active infection. Genome sequence data demonstrated that *C. trachomatis* possesses a type III secretion system, by which the organism injects effector proteins into the host cell at the attachment stage [40]. The total panel of injected proteins and their detailed functions in uptake into the host cells remain to be defined, but for one example, evidence for injection of a toxin encoded by the *C. trachomatis toxB* gene has been established [41]. Chlamydial TARP and other proteins function in the uptake/invasion process leading to sequestration of the organisms in their cytoplasmic inclusions [e.g., 42–45]. Interestingly, the gene designated CT622 on the genome sequence of *C. trachomatis* encodes a product which is injected into the host cytoplasm throughout the developmental cycle; loss of the encoded protein attenuates infectivity and intracellular development during the cycle [46]. Perhaps not surprisingly, chlamydiae manipulate host cell glucose transport via upregulation of *GLUT1* and *GLUT3*, and that upregulation is dependent on chlamydial protein synthesis [47]. Chlamydiae are dependent on iron acquisition from the host, and they have evolved unusual mechanisms to accomplish that uptake, although we do not fully understand those mechanisms, however [48]. Recent studies from several laboratories have demonstrated that chlamydial proteins strongly and directly influence host cell processes, to the advantage of the

pathogen. For example, the organism produces a protein designated CADD, which binds to host cell death receptors to influence the apoptotic process [49, see also 50]. Interestingly, a recent study identified a dual Lys63-deubiquitinase and Lys-acetyltransferase activities in the *Chlamydia* protein ChlaDUB1, and these activities lead to the breakup of the host cell Golgi apparatus [51]. All these manipulations of the host cell, either epithelial or monocytic, abet the ability of the pathogen to elicit joint disease. Reviews from a number of sources highlight these and other aspects of interaction with their immediate host cells by chlamydiae [e.g., 52, 53]. As developed in the following chapters, other bacterial pathogens also overt the host cell to their advantage.

Chlamydial infections elicit a strong inflammatory response, although that response is often more clinically apparent in men than in women, at least for urogenital infections. A major surprise from the various full-genome sequencing programs is that the chlamydial chromosome encodes not one, but three versions of the pro-inflammatory Hsp60 protein [40, 54]. The "original" gene, which is nearly identical to that from *E. coli* and other bacteria and which is well-known to be highly pro-inflammatory, is *groEL* (genome designation CT110), and it is found in an operon with groES, as in *E. coli* [40]. The other two Hsp60-encoding genes (CT604 and Ct755) are distantly linked to CT110. These three genes are the result of gene duplication events, although their sequences are not identical. The three Hsp60-encoding genes are expressed early in the developmental cycle, are transcribed fully independently of one another throughout that cycle, and show high levels of expression throughout the cycle [55]. These gene products are largely, although certainly not exclusively, responsible for eliciting the host inflammatory response, which includes high levels of production of IFN-γ, TNF-α, and other pro-inflammatory mediators. Host signaling pathways triggered during active chlamydial infection by other proteins from the bacterium have also been studied extensively [e.g., 56].

Strains/Serovars Involved in Arthritogenesis

As developed in Chap. 28, the incidence of *Chlamydia*-induced arthritis is relatively low following genital *C. trachomatis* infection; moreover, only about half of those who do develop the acute disease progress to chronicity (see [57–59]). *C. trachomatis* strains/serovars (originally defined serologically) are generally divided into ocular and genital groups. Serovars were differentiated as a function of the structure of the *ompA* gene product, and serovar-specific monoclonal antibodies to this protein were used to differentiate strains in infected tissue samples. More recently, serovars have been elucidated in clinical samples by DNA sequence of the cloned *ompA* gene, followed by in silico translation to determine the predicted amino acid sequence of the protein, [60, 61].

The ocular group includes serovars A, B, Ba, and C, and the genital group includes serovars D–K, plus the lymphogranuloma venereum group (LGV) [e.g., 19, 62]. The assumption has been that, since the inflammatory arthritis follows genital chlamydial infection, the inciting organisms must belong to the genital serovar group. We defined the DNA sequence of multiple cloned *ompA* genes from each of 36 patients with well-defined chronic *Chlamydia*-induced arthritis, in a study originally intended to assess sequence diversity at that locus within individual patient samples; as predicted, the diversity was low. We then asked which serovars were involved via comparison of our sequences to the known *ompA* sequences in the databases, and all sequences from each patient derived virtually exclusively from ocular group organisms [63].

We did identify a few cloned sequences in which some DNA exchange had taken place so as to give minor characteristics of genital serovar genome structure in the predominantly ocular serovar genome. The overall genome structure is somewhat different between ocular and genital group organisms at *ompA* and other chromosomal regions, and those differences are almost certainly responsible in some unknown fashion for the ability of ocular group organisms to disseminate from the genital system to the joint, once at that site to elicit severe inflammation. More detailed and extensive study of the genetic component of *C. trachomatis* infecting synovial tissue in additional patient samples must be done to elucidate the mechanism(s) underlying chlamydial dissemination from the urogenital system to the joint. Unknown attributes of the host genetic background must also influence dissemination to the joint in some individuals.

These differences either individually or in concert also must influence the remitting–relapsing phenotype of many patients with the chronic arthritis, again as developed in Chap. 28. The relatively low incidence of acute inflammatory arthritis among patients with a documented genital chlamydial infection may be a function of the presence or absence of ocular serovar organisms in the genital inoculum leading to infection. That is, infection of the human genital tract rarely if ever involves a clonal population of chlamydiae. Rather, the inoculum occasionally can include some serovar diversity, with a majority of such inocula including only one or more genital serovars and others, a minority, having a component (probably a small component) of ocular group organisms.

We suggest that the acute inflammatory arthritis develops only in that minority of patients whose genital inocula include ocular serovar organisms (for further discussion see [63]). However, this contention does not explain the observation that only approximately half of patients with the acute

disease progress to chronicity. The explanation for this almost certainly will be complex and center on genome sequence differences among the synovial population of infecting ocular organisms, as yet undefined aspects of the host genetic background, and the host–pathogen interaction that these genetic components engender. Elucidating these interactions and their genetic underpinnings will comprise experimental questions of significant interest for future studies. We note too that determination of whether cervical or urethral infections include a component of ocular serovar chlamydiae is one potentially useful approach to identifying patients at risk for development of the inflammatory arthritis.

Chlamydial Access to and Pathogenesis of the Joint

The elicitation of disease by a pathogen during primary infection often is just a preliminary for establishment of a longer-term relationship with the host [64, 65]. We and many and others have suggested that this is the case for genital infection by *C. trachomatis*, and it is also almost certainly true for ocular infections by this pathogen as well as pulmonary infection by *C. pneumoniae*. Production of chlamydial Hsp60 and other gene products during urethral or cervical infection elicits a number of responses from the host, including a Th1-type immune response [18, 19, 24, 62, 66–68]. Importantly, monocytic cells are attracted to the site of infection, where they take up elementary bodies with the purpose of disposing of them [e.g., 19]. However, following internalization of elementary bodies into the monocyte inclusion, the normal course of phagosome–lysosome fusion does not take place [26, 31, 69–73]. Instead, within the cytoplasmic inclusion, elementary bodies undergo the initial differentiation process to the reticulate body form; that is, transcriptome analyses over time during the first day post-infection of normal human monocytes in culture demonstrate that genes encoding products necessary for the differentiation to reticulate bodies are expressed as they are during the initial stage of normal active infection [19]. These include genes specifying components of the protein synthetic system, various transporters, proteins to be inserted into the inclusion membrane, the three Hsp60 proteins, and others. More than 200 genes encoding proteins, many of currently unknown function, are also expressed, and it is thought that many of these contribute to virulence and pathogenesis. Importantly, *Chlamydia*-infected monocytes are frequently extravasated from the genital tract, by which means they disseminate to other sites using the monocytes as a vehicle [26, 55, 67, 74].

During the hours after the differentiation process, chlamydiae within monocytic cells enter an unusual infection state designated "persistence" [26, 68, 75]. Data from patient samples and from studies of an in vitro model system of this state suggest that chlamydiae within the circulating monocytes reach the joint in the persistent state [26, 76]. That is, joint pathogenesis results from the biology of chlamydial persistence and the interaction of the organisms with the host cell in that infection state. Transcriptome analyses demonstrated that the transition from normal active infection to the persistent state often involves downregulated expression of many genes that are upregulated during the first 24 h post-infection, with adjustment of transcript levels for a panel of genes encoding lipid modification enzymes, ABC transporters, some components of the transcription and translation systems, and others [e.g., 70–72]. We identified no genes that were specifically or solely involved in transition to persistence for *C. trachomatis*; this is in contrast to the situation for other bacterial pathogens known to utilize a persistent infection phase, such as *Mycobacterium tuberculosis* and others [73].

Importantly, transcript analyses targeting the three Hsp60-encoding genes demonstrated high levels of expression for each during normal active infection, with expression levels of the CT604 and CT755 genes exceeding that of the authentic *groEL* (CT110) gene [55]. By contrast, studies of the monocyte model of chlamydial persistence demonstrated that transcript levels from CT604 were actually increased in that state, relative to their levels during active infection, but mRNA levels from CT755 were severely attenuated [55]. Indeed, even using extremely sensitive PCR screening systems, it was difficult to identify any transcripts from CT755 during established persistent infection. We confirmed that these data from the in vitro model system accurately reflected the situation in synovial tissue samples from patients with well-documented chronic *Chlamydia*-induced arthritis. Thus, the CT604 gene product probably functions in some manner to facilitate the transition to persistence, and attenuation of the level of the CT755 gene product during that transition indicated its possible function in maintaining the active infection state for chlamydiae [55]. These are contentions that must be demonstrated unequivocally.

Given that a significant host synovial inflammatory response is characteristic in patients with active chronic *Chlamydia*-induced arthritis, the CT110- and CT604-encoded Hsp60 proteins probably are involved in eliciting the synovial inflammatory response, whereas the CT755 gene product is not. Further, given the insertion of chlamydial proteins into the inclusion membrane and into host cell itself via the type III secretion system and other means during the infection process (see above), chronic synovial pathogenesis and its consequent inflammation must result from an extensive process of host–pathogen interaction. We view this interaction as a sort of molecular genetic conversation between pathogen and host cell that ends in a balance, which we understand as persistent long-term chlamydial infection of synovial tissue. We currently have little detailed understanding of that conversation,

but transcriptome analyses that are currently underway, and use of the new systems for modulation of chlamydial gene expression, will be critical in sorting out these details.

Remitting–Relapsing *Chlamydia*-Induced Arthritis

Many patients with chronic *Chlamydia*-induced arthritis display a remitting–relapsing disease phenotype, with quiescent periods of disease lasting for weeks to years in some cases [17, 18, 58, 59, 76; see also Chap. 28]. Virtually, all clinical samples that we and others have analyzed over many years were obtained from individuals in the active disease phase. We have, though, examined a small number of chlamydial and host gene expression issues during quiescence in samples from a few patients with documented chronic *Chlamydia*-associated arthritis [10]. We first asked if the organism is present in synovial tissue during quiescent disease, and quantitative PCR assays targeting the chlamydial chromosome in those samples indicated that the organism indeed is present; the bacterial load is several-fold lower during remission than during active disease. Interestingly, however, assessment of transcript levels from the three Hsp60-encoding genes in those samples showed that mRNAs from CT110 and CT604 were at or above levels seen in chlamydiae during active disease; transcripts from the CT755 gene were low in the quiescent disease samples, as in samples from those with active disease [10, 77]. Host cell mRNA encoding IL-10, IFN-γ, and TNF-α were below levels in synovial tissue samples from patients with active disease, but mRNA encoding MCP-1 and RANTES were either at about the same level as in active disease or in the case of the latter, significantly higher in some samples [10, 77, 78]. No data regarding the histopathology of the samples from patients in quiescent disease was available. While these data provide information regarding chlamydial and host genetic behavior during quiescent disease, they provide no insight into why remission was the case. Although the infecting organisms were present in the samples at relatively low levels in the quiescent disease samples, they were still producing high levels of mRNA encoding the two relevant Hsp60 proteins; the host response was not significantly attenuated from that reported in tissues from patients suffering active disease, at least in terms of messengers encoding pro-inflammatory cytokines and chemokines. Clearly, the simplest explanation of quiescence cannot be the case, i.e., that chlamydiae are in some dormant, totally inactive state during remission and that inflammatory molecules therefore are not present in the synovium. The true explanation for remission, and any strategy to exploit aspects bacterial or host behavior for therapeutic purposes, must await further investigation.

Summary

Significant progress has been made in understanding mechanisms of chlamydial pathogenesis during both primary active infection and persistent infection following dissemination to distant sites such as the synovium. As with the study of synovial pathogenesis elicited by other bacterial (and other) pathogens, much of this increased knowledge has resulted from studies of the basic biology of the organisms. In the case of chlamydiae, this includes elucidation of genome structure and differences in such structure among strains/isolates and among chlamydial species, which provides understanding that chlamydiae can and do sometimes exchange genetic information, accounting for some genome structure differences; detailed large-scale gene expression studies, extensive cell biological analyses to illuminate details of influences of the pathogen on its host cell, and vice versa will be required to provide a full picture of the pathogenesis process. It is clear that the host–pathogen interplay during both normal active and persistent infections is complex for chlamydiae, and we assume for other pathogens, and that further understanding of its complexities will be required before new avenues of therapeutic approach can be envisioned and productively pursued. Regarding *Chlamydia*-induced arthritis, the bacterial products that elicit the characteristic inflammatory response in the joint are being defined, and further insights into the nature and specific effects of those gene products on the host will inform current and future treatment options. Of potentially significant interest is the initial insight into the genetic behavior of pathogen and host during the remitting phase of the chronic arthritis, since if molecular details underlying the transitions between active and quiescent disease can be exploited, it should provide a means by which disease development or relapse can be manipulated to advantage. Progress has been made in treatment in terms of combination antibiotic therapy (again, see Chap. 28), as a function of identification of the nature of the chlamydial strains/serovars that appear to be the specific causative agents for disease development, and in terms of bacterial genetic and related strategies for entry into the persistent infection state [e.g., 73, 79].

A significant question at this point concerns the sources from which new insights will come vis-à-vis chlamydial pathogenesis and host–pathogen interaction. We contend that one potentially fruitful source will result from the development of systems for genetic manipulation of growing *C. trachomatis*, its related pathogens, and others [see 80–82]. Productive means of genetic manipulation of these organisms and others are becoming available, which will expand importantly our means of analysis of host–pathogen interaction [see e.g., 83]. Of course, a panel of well-developed genetic and biochemical methods already exist for the assessment of host cell responses to both active and persistent

chlamydial infection. Certainly, study focused on these aspects of host biology must be an integral part of any research program to develop new strategies for anti-*Chlamydia* therapies. Thus, given new experimental tools and the fresh points of view concerning pathogenesis that they provide, the control of both active and persistent chlamydial infections as they operate to induce inflammatory arthritis should be amenable to clinical control. We expect that these same strategies will be applicable to elucidation of the molecular details underlying joint pathogenesis elicited by bacteria other than chlamydiae, as well as other microbial pathogens.

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Microbiome and Microbiota in Rheumatic Disease

2

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Introduction

For centuries, the term bacteria had a negative connotation in regard to human health [1]. Many diseases and disorders that have plagued the human population throughout history (from tuberculosis to meningitis to cholera) are caused by the infections driven by different bacterial, fungal, and viral species. However, over the past couple decades, there has been a paradigm shift in the understanding of the relationship between these microbes and human beings. Research shows that bacteria, along with the fungi, eukaryotes, and viruses that inhabit the human gastrointestinal tract (collectively called the gut microbiota), play an essential role in human survival and ecological success [2]. The gut microbiota works in influencing multiple aspects of our health. This includes nutrient and drug metabolism as well as our body's overall immune maturation and response. The widespread influence of the gut microbiome has led it to being coined the virtual organ of the body and our second genome [3, 4].

Supported by:
NIH/NIAMS R03AR072182, the Colton Center for Autoimmunity, Rheumatology Research Foundation, the Riley Family Foundation and the Snyder Family Foundation (Scher).

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Physiological Concepts

Methods to Study Microbiota

While often used interchangeably, there is an important distinction between the term's microbiome and microbiota. The microbiota is the dynamic collection of all microorganisms in a defined environment, such as the gastrointestinal tract [5]. The collection of all the genomes of the microbiota is the microbiome. Current characterization of the bacterial communities in the intestinal microbiota is made possible through the application of a variety of clinical and genome sequencing techniques. The most commonly used techniques are outlined in Table 2.1. Stool samples or intestinal biopsies are collected from individuals and are used to identify intestinal microbiota [7]. Subsequently, initial sequencing of the microbiota most often involves taxonomic characterization using 16S ribosomal ribonucleic acid and sequence variants for bacteria [8]. Next generation sequencing platforms look at hyper-variable, or highly polymorphic, sites in the 16S region to differentiate between bacterial species [8]. Sequencing errors can make it difficult to distinguish between differences in the 16S sequences and sequencing artifacts. Operational taxonomic units (OTU) are used to overcome this issue, but they lead to a decrease in taxonomic resolution. Recent technological improvements have led to the development of de-blur and de-noise programs such as QIIME2 and DADA2 [9]. Sequencing data then goes through bioinformatic analysis to clean the data and derive desired parameters, such as alpha diversity, beta diversity, and relative abundance [10].

Metagenomic analysis of DNA that codes for modules, enzymes, and pathways further enhances our understanding of functional capabilities of the microbiome. Functional profiles from the OTU datasets are predicted through use of reference databanks, including SILVIA, Kyoto Encyclopedia of Genes and Genomes (KEGG), Ribosomal Database Project, and RNAcentral [11–14].

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_2

Table 2.1 Techniques commonly used to profile microbiota [6]

Name	Methodology	Techniques
Biomarker sequencing	The study of sequence variations. In the study of gut microbiota, 16S ribosomal ribonucleic acid analysis is used	NGS (next generation sequencing)
Metagenomic analysis	Study of function of genetic material in a microbe	NGS (next generation sequencing)
Metatranscriptome analysis	Study of gene expression at the RNA level	NGS (next generation sequencing)
Metabolome analysis	The study of metabolite (end products of cellular processes) formation by microbiota populations	Gas chromatography Mass spectrometry High-performance liquid chromatography Capillary electrophoresis

The study of viral populations differs from bacterial microbiota. In order to isolate VLPs (virus-like particles), collected samples undergo general filtration and centrifugation steps in order to remove particulate matter as well as bacterial and human cells. Further filtration steps include the use of cesium chloride density gradient centrifugation to more thoroughly remove any host-derived DNA for effective VLP enrichment [15]. Isolated VLPs are then treated with DNase and RNase to degrade free nucleic acids, and the viral genomes are extracted using DNA/RNA purification techniques, most commonly the standard phenol-chloroform method [16]. Analysis is done through metagenomic analysis, as described; viral sequence data is clustered into groups called "contigs," which allows for sensitive detection of sequence homology through reference to current viral databases [17]. Study of fungal communities, collectively known as the mycobiome, is a rapidly emerging field. Current understanding of the mycobiome lags far behind that of the bacterial microbiota. Techniques to study these communities has greatly evolved over the past couple decades. Presently, next generation sequencing is used to analyze 18S, 5.8S, and 28S ribosomal ribonucleic acid regions [18].

Gut Microbiota Composition

Originally thought to only house a few hundred bacterial species, recent studies have estimated that the human gut microbiota is composed of over 1000 bacteria populations [19]. Overall, a healthy adult microbiota is dominated by the phyla *Bacteroidetes* and *Firmicutes*, followed by smaller populations from the phyla *Actinobacteria* and *Verrucomicrobia* [20]. There is high variability between individuals – while the diversity is currently unexplained, differences in diet, environment, host genome, and early microbial exposure have all been implicated [21]. It is important to note that there is also high variability between different parts of the gastrointestinal tract, as noted in Table 2.2.

Table 2.2 Communal microbiota of GI tract [22]

Area of GI tract	Common bacterial populations
Oral cavity	*Streptococcus*
	Neisseria
	Gemella
	Granulicatella
	Veillonella
Esophagus	*Streptococcus*
Stomach	*Helicobacter pylori*
	Streptococcus
	Prevotella
Small intestines	*Streptococcus*
	Bacteroides
	Clostridium
Large intestine	*Bacteroides*
	Prevotella
	Ruminococcus

Development of Gut Microbiota

The development of the gut microbiota is widely accepted to begin immediately after birth. Following birth, an array of factors affects the colonization of the infant intestine, including gestational age, mode of delivery, diet, and antibiotic treatment [23]. Facultative anaerobes first colonize the gut and alter the environment to allow for further colonization by the bacterial phyla *Actinobacteria* and *Proteobacteria*. Further changes in diet, illness, and medications cause the infant microbial populations to undergo rapid change until roughly age 2, when they resemble the composition of an adult's microbiota [24].

Resilience of Gut Microbiota

Although the composition of the intestinal microbiota can vary between individuals, its makeup within the individual generally remains stable and resistant to change. However, changes in factors such as diet and antibiotic use can greatly affect microbial populations. Given the correlation between a healthy microbiota and maintenance of human health, it is possible that changes in microbiome features can be used to control dysbiosis-related disease processes. Research on the effects of diet is particularly relevant due to its ease of modification. Studies have shown that long- and short-term changes in diet have varying effects on the microbiota. Variability in dietary habits due to global and cultural influences correlates with differences in microbial composition. Individuals that eat protein-rich diets show enrichment in

Bacteroides while those that eat carbohydrate-rich diets show enrichment in genus *Prevotella* [25]. On the other hand, a study comparing the effect of high fat/low fiber diet versus low fat/high fiber diets on microbiome composition in 10 days indicated that although changes in bacterial composition occurred rapidly, there was no long-term alteration [26]. Further research is needed to better understand the links between diet and microbiome composition.

There is also substantial evidence that antibiotics can cause changes in composition of gut microbiota. One of the most common microbiota-associated diseases caused by antibiotic use is C. difficile, a pathogenic infection first seen in developed countries such as the United States. Overuse of clindamycin, a broad-spectrum antibiotic, can decrease bacterial variety in the gut microbiota, reducing resistance to pathogen colonization. This can lead to pseudomembranous colitis due to overgrowth of Clostridium difficile [27]. Vancomycin, a glycopeptide antibiotic used as treatment for C. difficile, also induced dramatic and long-lasting perturbations in intestinal microbiota. This treatment is shown to greatly diminish microbiota richness. Levels of the *Bacteroidetes* phylum were greatly reduced, and levels of some *Firmicutes* and *Proteobacteria* phylum, thought to be associated with human infections, increased [28]. Another study found that amoxicillin greatly decreased levels of colonic anaerobic and aerobic bacteria through reduction in MHC class I and II gene expression in *Lactobacillus*, reducing AMP expression and increasing mast cell protease expression [29]. Changes in the microbiota due to antibiotic use can also affect immune response to viral infections. Antibiotic use decreases production of pro-cytokines pro-Il-1B and pro-IL-18, both of which contribute in the defense against influenza virus [30]. Even though antibiotics can have a negative effect on our microbiota, and consequently our immunity and health, avoiding usage is not feasible. Current measures to counteract the negative effects of antibiotics include use of probiotics and bacterial ligands to improve immune tone and supplement any deficits in the microbiota [29].

Functions of Gut Microbiota

The human gut microbiome carries out a variety of functions that have a beneficial effect on our health. These duties can be split into three physiological categories, each of which is discussed below.

Metabolic Function

The human gastrointestinal tract is equipped with the proper machinery to break down the majority of our dietary molecules, such as monosaccharides and disaccharides. The gut microbiota helps in the metabolism of more complex molecules such as polysaccharides, lipids, and proteins. Complex carbohydrates are broken down by these bacteria into byproducts called short-chain fatty acids (SCFA). The three SCFA that pre-dominate in the human gut are propionate, butyrate, and acetate. SCFA are taken up by gastrointestinal epithelial cells, where they then are involved in a variety of cellular processes, including gene expression, energy metabolism, and cell differentiation [5] as well as body-wide processes such as appetite regulation [31]. Butyrate and propionate in particular have a variety of functions related to human metabolism. Butyrate has anti-inflammatory [32] and anti-cancer functions, affects tight-junction formation in the formation of the gut barrier, and acts as a histone deacetylase inhibitor in regulations of gene expression [33]. Propionate acts as a regulator of gene expression through a similar mechanism to butyrate but also attenuates eating behaviors through the reward-based striatal neural pathways [34].

Nutrition

Gut microbiota also plays an important role via nutritional support of the host through the de novo synthesis of essential vitamins and amino acids for maintenance of homeostasis. *Bifidobacteria* produce folate, and lactic acid bacteria produce vitamin B12. Vitamins such as menadione and coenzymes Q1–Q3 inhibit pathogen growth [35], and B vitamins increase gut non-specific resistance through enhancing the activation and proliferation of neutrophils, monocytes, and macrophages [36]. While most amino acids in the intestines originate from the metabolism of dietary proteins, a small proportion is synthesized de novo. Roughly 2–20% of circulating lysine in the plasma and urine originate from the gut microbiota [37]. The intestinal microbiota also produces D-amino acids, which are used in the composition of bacterial walls and bacterial peptidoglycans and affect biofilm formation [38].

Immune System

The intestinal tract houses more immune cells than any other areas of the body. As a result, the gut microbiota is inherently tied to the development and maintenance of the immune system as well as the acting as a protection mechanism against pathogen invasion. Development of the immune system starts from birth. As previously mentioned, mode of delivery for an infant is an important effector of gut microbiota development. Research indicates that children born from C-section have higher risk of developing diabetes, asthma, and obesity in comparison to vaginally born children [39]. In addition, a recent animal model study found that mice raised in gnotobiotic environments were

at higher risk of inflammatory disorders, including asthma and IBD. Abnormal microbial development leads to defects in immunological function and intestinal barrier, which leads to inflammation and higher risk for the development of disorders such as obesity, Crohn's disease, and diabetes [40].

Microbiota in Disease Processes

Alterations in gut microbiota have been associated with a large array of diseases, ranging from arthritis to obesity to diabetes. Table 2.3 below outlines changes in the microbiota associated with each disease process.

Obesity

Obese patients show dysbiosis characterized by lesser diversity and richness of bacteria. Studies on animal models have shown an increase in *Firmicutes* and decrease in *Bacteroidetes*, regardless of dietary intake [41]. These differences in microbial profiles have been shown to affect body weight. A recent study revealed that germ-free mice that received fecal bacteria from obese women gained weight and developed metabolic complications similar to those found in obese patients [51].

Table 2.3 Synopsis of microbiota changes in disease processes

Disorder	Effect on host microbiota	Reference
Obesity	Increase in SCFA generation Increase in *Firmicutes* Decrease in *Bacteroidetes*	[41, 42]
Type 1 diabetes	Increase in genus *Clostridium*, *Bacteroides*, and *Veillonella* Decrease in *Firmicutes*/*Bacteroidetes* ratio Higher levels of circulating LPS	[43–45]
Spondyloarthritis	Increase in family *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae* Decrease in family *Veillonellaceae* and *Prevotellaceae*	[46]
Psoriatic arthritis	Decrease in RANKL and MCFA levels Changes in genus *Pseudobutyrivibrio*, *Ruminococcus*, and *Akkermansia* populations	[47]
Rheumatoid arthritis	Decrease in genus *Bacteroides* in NORA patients Increase in species *Prevotella copri* in NORA patients	[48]
Systemic lupus erythematosus	Decrease in family *Lactobacillaceae* Increase in family *Ruminococcaceae*, *Rikenellaceae*, and *Lachnospiraceae* Decrease in *Firmicutes*/*Bacteroidetes* ratio	[49, 50]

Obese patients show increased levels of SCFA generation, which is thought to increase triglyceride (TAG) accumulation through multiple molecular pathways. SCFA activates sterol regulatory element-binding transcription factor 1 (SREBP1) and carbohydrate responsive element-binding protein (ChREBP), both of which are involved in lipogenesis. SCFA also suppresses fasting-induced adipocyte factor, which inhibits lipoprotein lipase to inhibit TAG breakdown, causing accumulation in adipocytes [42].

Type I Diabetes

Type I diabetes is an autoimmune disease characterized by lack of insulin production due to T-cell-mediated destruction of pancreatic beta islet cells. Studies have shown that the ratio of *Firmicutes* to *Bacteroidetes* is lower, and there are higher levels of *Clostridium*, *Bacteroides*, and *Veillonella* [43]. Higher circulating levels of lipopolysaccharide (LPS) are also found, which work in increasing pro-inflammatory cytokines and impairing pancreatic beta-cell function [44]. Destruction of the intestinal mucosal barrier due to changes in microbiota composition leads to leakage of LPS, which causes activation of toll-like receptor 4, a key molecule in the maintenance of innate and adaptive immunity [45].

Spondyloarthritis (SpA)

Spondyloarthritis is a group of inflammatory conditions with shared features of enthesitis, colitis, uveitis, axial skeleton arthritis, and dermatologic and HLA-B27 involvement. One study found that HLA-B27 transgenic rats grown in a germ-free environment do not develop key arthritic features such as colitis and arthritis. Intriguingly, it was found that the re-introduction of a normal gut microbiota caused the inflammatory features to reestablish themselves [52]. These transgenic mice have higher levels of *Paraprevotella* and lower levels of *Rikenellaceae* [53]. Further studies found that in addition to dysbiosis, there is dysregulated expression of AMPs and bacteria-specific IgA. These changes are associated with enhanced Th17 and Treg, leading to arthritis development [54]. There is also significant effect on metabolite levels, particularly MCFA and SCFA. Treatment of HLA-B27 transgenic mice with SCFA propionate attenuated the development of inflammatory disease [55]. Similarly, the ankylosing enthesopathy (ANKENT) mice, which spontaneously develop enthesitis and ankylosis, do not develop the phenotype when grown in a germ-free environment [56, 57]. A third example is found in the SKG mouse, which develops a spontaneous SpA-like syndrome due to the impairment of ZAP-70, a T-cell signal transduction molecule. SpA features are also absent when these mice

are reared under germ-free conditions or with treatment of antifungals [49]. In. fact, treatment of germ-free SKG mice with fungal B-glucans (i.e., curdlan and laminarin) provokes arthritis and colitis [58]. In humans, studies have shown that patients with ankylosing spondylitis have higher populations of *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae* and lower abundance of *Veillonellaceae* and *Prevotellaceae* [46].

Psoriatic Arthritis

Psoriatic arthritis is a rheumatologic disorder that also falls under the larger category of chronic SpA. While its pathogenesis currently remains unclear [59], there has been much interest in understanding the role of the gut microbiota in PsA disease processes. Preliminary studies have shown that PsA is associated with perturbations in microbial populations, particularly the genera *Pseudobutyrivibrio*, Ruminococcus, and *Akkermansia*, as well as a marked decrease in gut lumen RANKL and MCFA levels [47].

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease caused by genetic and environment factors and characterized by generation of autoantibodies and multi-joint destruction of bone. While recent research has shown over 100 genetic susceptibility loci associated with RA, the environmental factors are not fully understood [60]. It has been increasingly thought that the gut microbiota is a critical environmental factor in the development of rheumatoid arthritis. Multiple animal studies have strengthened the correlation. Interleukin-1 receptor antagonist knock-out mice (IL1rn-/-) spontaneously developed T-cell-mediated arthritis under pathogen-free conditions due to excessive Il-1 signaling. Although arthritis development was not induced in mice grown under germ-free conditions, recolonization with *Lactobacillus* induced the arthritis through the activation of toll-like receptors [61]. Another study looked at DBA1 mice (mouse model for RA where immunization with collagen leads to development of arthritis). It was found that mice raised in germ-free conditions and colonized with microbiota from collagen-induced arthritis (CIA) mice were at higher risk for development of inflammatory arthritis than those treated with the microbiota of CIA-resistant mice [62]. The gut microbiota has also shown to be involved in human RA. Patients with new onset RA (NORA) were found to have increased amounts of *Prevotella copri* and reduced levels of *Bacteroides* in the gut microbiota. Another study looking at RA patients in China found increased levels of L. salivarius in the gut and *P. copri* in the gut for the first year after disease onset [48].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease characterized by the generation of autoantibodies and the production of pro-inflammatory cytokines, which leads to persistent inflammation and systemic tissue damage. Lupus is also a sex-specific disease, occurring in more women than men. Animal studies of lupus-prone mice (MRL/lpr) showed significant reduction of *Lactobacillaceae* with concomitant increase in *Ruminococcaceae*, *Rikenellaceae*, and *Lachnospiraceae*. Further studies showed differences in gut microbiota between sexes – female MRL/lpr mice had higher levels of *Lachnospiraceae* and *Bacteroidetes* and lower levels of *Bifidobacteria* and *Erysipelotrichaceae* when compared to MRL controls. In males, there were no significant difference when comparing the two strains. These differences in bacterial populations may indicate differences in severity of lupus symptoms, age of onset [50]. Human studies, currently few and far between, show a decrease in *Firmicutes*/*Bacteroidetes* ratio in SLE patients when compared to healthy controls [49].

Microbiome Modulation

It is becoming increasingly recognized that the microbiota has wide-ranging effects on our health and that alterations in the microbiota can result in a variety of diseases such cancer, obesity, and several rheumatological disorders. While current research is shedding light into the potential uses of the microbiome for disease diagnosis and therapy, there are multiple avenues that still need to be explored. Four main areas are presented below.

Diet

Multiple recent studies have shown that diet affects the microbiota to influence an individual's health. Each of the major macronutrients and many micronutrients have been shown to affect the gut microbiota [63]. Because nutrients are not consumed in isolation, there is a need to examine the effects of broader dietary patterns, which can provide valuable information on effective nutrient ratios. This information in turn can be used to work toward designing individualized probiotic-based dietary interventions to treat disorders such as IBD and arthritis. Before such treatments can become widespread, there are multiple fundamental questions regarding diet and the microbiome that need to be answered. It has been widely established that the microbiome has high plasticity in the short-term, but long-term studies indicate stable microbial populations resistant to change [20]. In addition, the overall degree of plasticity depends on previous dietary patterns [64]. However, many of the prior microbiota studies that formed

the foundation of our current understanding were performed in animal models. Additional human studies are needed as the field pursues the development of microbiome-based treatments [65].

Pharmacomicrobiomics

The field of pharmacomicrobiomics is a rapidly evolving area of research interested in understanding how individual variations in the intestinal microbiome modulates host response to the action, disposition, and toxicity of drugs [66]. A long-term goal of this discipline is the manipulation of microbial populations and their metabolites to improve drug efficacy.

Most of the initial work in pharmacomicrobiomics has been pursued in immune-oncology studies. A study that looked at correlations between microbiota composition and outcomes in patients with metastatic melanoma receiving check-point inhibitors (i.e., ipilimumab) found that overabundance of *Bacteroidetes* correlated with resistance to colitis development [67]. Later studies found that the anti-cancer effects of ipilimumab, a CTLA-4 blocker, relied on the presence of specific gut microbiota [68]. This emerging interest in pharmacomicrobiomics spread to the study of treatment of rheumatic diseases. Azo-bonded pro-drugs such as sulfasalazine (SSZ) and mesalamine require intestinal microbiota to become active compounds. While these enzymes are universally found in the microbiota, their individual abundance and activity can differ widely [69]. Additionally, metabolites derived from azo reductions are metabolized by the gut microbiome, and the active drug efficacy is also variable between individuals [70], lending credence to the importance of the microbiome in drug efficacy.

Another key example can be seen in the treatment of RA. Despite advances in the understanding of RA pathogenesis, methotrexate (MTX) remains an important drug in the treatment of RA and other autoimmune disorders. However, over 50% of patients with moderate to severe RA show little to no improvement in symptoms with oral MTX use [71–73]. Although the reason for variations in clinical response remains unclear, recent studies indicate that it may be partially driven by individual differences in the gut microbiota. Animal studies looking at germ-free and antibiotic-treated mice found decreased levels of MTX metabolism compared to controls [74, 75]. Another study that analyzed the enzymatic function of gut microbiota in new-onset RA patients (NORA) found variation in bacteria-derived metabolic pathways, further suggesting interindividual differences in microbial composition [76]. Further studies observed that MTX can impact the composition of the microbiota, partially through the direct reduction of specific bacterial populations [77]. These results also show that MTX may work through the modulation of the gut microbiome in RA patients, supporting the importance of pharmacomicrobiomics for this and related anti-rheumatic drugs.

The gut microbiome is therefore emerging as an important player in personalized medicine with several recent reports showing the relevance of the gut microbiome on drug efficacy and toxicity [78–81]. However, due to great diversity of microbial makeup, its broad function in the host, and the complex drug-diet-microbe-host interactions, a systems-based approach is required to further understand the basic mechanisms. Recent advances in bacterial culturomics and high-throughput technologies, together with large databanks, high-computing power, and biocomputing tools, to analyze vast amount of individual patient consecutive data information collected over a period of time will enable the development of the next phase in personalized medicine [82, 83].

Fecal Material Transplantation

Fecal material therapy (FMT), or the transfer of intestinal microbiota from a healthy donor to a patient, has recently received broad attention as a potential treatment for a variety of inflammatory diseases. A fecal suspension can be administered in a variety of ways, including nasoduodenal tube, colonoscope, enema, or capsule [84]. One of the first clinical uses of the technique was in 1958, where fecal enemas were used in the treatment of pseudomembranous enterocolitis [85]. FMT is currently best known for its great success in treatment of *Clostridium difficile* infection [86]. FMT efficacy in the treatment of IBD is more mixed. Several smaller-powered studies show a reversal of symptoms. One non-randomized study found that colonoscope FMT in patients with chronic ulcerative colitis (UC) showed changes in microbiota composition, but no change in clinical symptoms [87]. A more recent randomized, placebo-controlled trial, which randomized patients with mild to moderate UC to either FMT or a placebo, found that 27% of FMT patients had clinical remission when compared to 8% of the placebo patients [88]. The application of FMT in rheumatic disease is currently in its infancy. An initial proof of concept clinical trial to establish the efficacy of FMT in patients with inflammatory rheumatic diseases is taking place in Denmark. In this six-month triple-blind study, PsA patients undergoing methotrexate (MTX) treatment will be randomized to receive either FMT or a placebo. Outcome assessments will be based on rheumatology follow-up at 3- and 6-month marks [89].

While current developments look promising, there are still many unknowns with FMT usage. First and foremost, standardization regarding what represents a positive outcome is needed to allow for more accurate comparison between trials. In addition, there is a lack of concrete guidelines for FMT usage. The expansion of FMT programs at

hospitals in addition to home preparation FMT video guides has outpaced the understanding of long-term treatment outcomes and overall safety. There also lacks universal guidelines for stool donor selection – current donors are selected more by trial and error than through clinical criteria [90].

Microbiome-Derived Metabolites

Our intestinal microbiota is metabolically active and produces multiple bioactive metabolites, such as bacteriocins, fatty acids, and vitamins. These molecules participate in a variety of physiological processes, from cell-cell communication to the reduction of intestinal inflammation to acceleration of weight gain [37]. Bacteriocins are a protein product thought to help in the inhibition of pathogen growth. Microbiota-derived short chain fatty acids (SCFA) maintain the gut barrier by promoting the differentiation of intestinal epithelial cells and inducing the formation of antimicrobial peptides [37, 91, 92]. Microbiota-derived vitamins work to activate the gut immune response. The study of microbiome-derived metabolites is still relatively new. Future work is needed to discover the most biologically active metabolites and the genes that encode them. These are important steps in the development of future treatments that specifically target therapeutic microbial communities and their derived metabolites. In addition, current studies involving microbiome metabolites are in vitro studies – future research should be directed toward in vivo analysis to better understand their effects.

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Gonococcal and Nongonococcal Bacterial Infections

3

Ignacio García-De La Torre
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Acute inflammation of one or more joints is a common cause of emergency medical evaluation, being one of the most important reasons for suspecting septic arthritis. Delayed or inadequate treatment can lead to irreversible joint destruction. Most septic arthritis is caused by bacterial infections. The most common cause of acute bacterial arthritis is gonococcal or nongonococcal infection of the joints. The term acute bacterial arthritis usually denotes not only most of the bacterial arthritis's caused by bacterial infection but also those caused by fungal and mycobacterial infection. This chapter is a review of the risk factors, pathogenesis, clinical manifestations, diagnosis, and treatments of nongonococcal and gonococcal arthritis. Other infections associated with arthritis, such as prosthetic joint infections and fungal and mycobacterial arthritis, have unique clinical manifestations and will not be covered in this chapter.

Nongonococcal and gonococcal arthritis are the most dangerous and destructive forms of acute arthritis. They are usually curable, but their associated morbidity and mortality are still significantly high in patients with prosthetic joints, patients with underlying rheumatoid arthritis, elderly patients, and patients with multiple severe comorbidities [1].

Risk Factors

The existing experimental evidence suggests that healthy joints are very resistant to infections, in contrast with diseased and prosthetic joints. Recognizing the influence of systemic, local, and social risk factors is of crucial importance. These factors increase the risk of bacteremia or reduce the body's ability to eliminate infectious organisms from the joint [2, 3].

Systemic disorders that affect the host's response by impairing the immune system include diabetes mellitus, pre-existing rheumatoid arthritis, liver disease, chronic renal failure, malignancies, intravenous drug abuse, hemodialysis, alcoholism, acquired immunodeficiency syndrome, hemophilia, organ transplantation, and hypogammaglobulinemia [4–8].

Local risk factors, such as damage of a specific joint, may be the result of earlier trauma, which in turn may be related to acupuncture procedures, joint surgery, or arthroscopy. The presence of cutaneous ulcers, skin infections [9], a prosthetic knee or hip joint, or previous damage to the joint architecture caused by rheumatoid arthritis, osteoarthritis, or crystal arthropathies (e.g., gout) [10] is an important predisposing factor for septic arthritis. Age is another important factor; newborns and elderly people, especially those older than 80 years, are particularly vulnerable [11–16]. Social risk factors include low socioeconomic status and occupational exposure to animals with brucellosis [17] in patients that inhabit regions where this zoonosis is still a public health issue [18]; furthermore, certain racial groups are significantly at higher risk of acquiring tuberculosis (e.g., people from India) [19].

Tuberculosis reemerged in developed countries in recent decades as a result of mass immigrations from endemic areas elsewhere, increasing the numbers of immunocompromised individuals, which also include those with AIDS. There has also been an increase in infection rates associated with drug abuse, homelessness, therapeutic noncompliance, and the emergence of drug-resistant mycobacteria [20]. Intravenous drug users are high-risk subjects and are more likely to have fungal, polymicrobial, or septic arthritis, which are much less frequent in the general population [21]. In some cases, these risk factors are compounded, meaning, for example, that patients with rheumatoid arthritis treated with immunosuppressive medications or steroids are at higher risk of

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_3

infection. Sometimes it is difficult to distinguish between an infection and inflammatory synovitis, especially when the patient is receiving steroid therapy.

A study in the Netherlands identified risk factors for bacterial arthritis. In almost half of the patients, bacterial infections were present in abnormal joints. More than 25% of the infected joints in patients with available clinical information contained prosthetic or osteosynthetic material. All but one of 22 adult patients with hip infection had a prosthesis. About 20% of the adult had rheumatoid arthritis; those patients accounted for 5 of 16 polyarticular cases. The authors of the study looked for clinical factors that would be amenable to prophylaxis. Infected skin lesions, which were present in 38 of 60 adult patients with an identifiable infection source, were considered the most common cause of hematogenous bacterial arthritis in patients with rheumatoid arthritis (16 of 22 cases). Invasive nonsterile medical interventions in places distant from the affected joints accounted for seven cases, all but one in native joints [22, 23].

An Italian study [24] drew attention to the fact that the reported incidence of septic arthritis varies from 2 to 5 cases per 100,000 persons per year among the general population to 70 cases per 100,000 persons per year among patients with rheumatoid arthritis. Indeed, individuals with rheumatoid arthritis are at particularly high risk of developing septic arthritis. This may be due to several reasons: diseased joints are more prone to bacterial colonization and rheumatoid arthritis (RA), while the prescribed treatments with corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biological therapies can have a negative effect on the immune functions required for protection against pathogens. Steroids and DMARDs seem to affect the synovial leukocyte count, and the leukocyte count in the synovial fluid of RA patients with septic arthritis is indeed lower than in patients with septic arthritis without underlying rheumatic diseases. It can be difficult to diagnose septic arthritis in RA patients because the development of a hot, painful joint is often mistaken for a relapse of the underlying joint disease, leading to a delayed diagnosis.

Common Risk Factors for Septic Arthritis [25]

- Systemic disorders
  - Rheumatoid arthritis
  - Diabetes mellitus
  - Liver diseases
  - Alcoholism
  - Chronic renal failure
  - Malignancies
  - Intravenous drug abusers
  - Hemodialysis patients
  - Acquired immunodeficiency syndrome
  - Hemophilia
  - Organ transplantation
  - Hipogammaglobulinemia
  - Immunosuppressive drugs and glucocorticosteroids
  - Biologic agents
- Local factors
  - Direct joint trauma
  - Recent joint surgery
  - Open reduction of fractures
  - Arthroscopy
  - Acupuncture procedure
  - Rheumatoid arthritis in a specific joint
  - Osteoarthritis
  - Prosthetic joint in knee or hip
- Age: elderly >80 years old or newborns
- Social factors
  - Occupational exposure to animals (brucellosis)
  - Low social income: tuberculosis

Pathogenesis

Septic arthritis is usually the result of direct inoculation or of an occult bacteremia that spread to the joint. The synovium is a highly vascular tissue with no basement membrane beneath the intimal layer, which makes it vulnerable to bacteremia [26]. Microorganisms such as staphylococci and streptococci may gain access to the bloodstream from their initial innocuous location when the integrity of the skin and the natural mucosal barriers is disrupted by injury or disease. Gram-negative septic arthritis is probably caused by bacteremia from the gastrointestinal or urinary tracts. Some bacteria, such as *Neisseria gonorrhoeae*, are particularly likely to infect a joint during a bacteremia episode [27]. In some cases, septic arthritis is the result of penetrating trauma such as bite wounds, foot injuries caused by stepping on nail, or an errant injection in drug users. Penetrating traumas, including those caused by plant thorns and wood slivers [28], are the most common means of infection of the small joints of hands and feet [22].

Arthroscopy and therapeutic joint injections with corticosteroids are sometimes, but rarely, complicated by septic arthritis. Furthermore, bacteria may gain access into the joint during joint surgery. Orthopedic surgeons often encounter patients with joint infections that are the result of trauma or surgical procedures. Examples include the accidental introduction of foreign bodies into a joint, arthroscopic surgery, open reduction of fractures involving joints, and arthroplasties [29]. Most cases of septic arthritis are caused by gram-positive bacteria. Enteric gram-rods

account for 43% of community-acquired bacteremia, but only for 10% of septic arthritis cases [30, 31].

This is likely due to the superior ability of gram-positive bacteria to bind to connective tissue and extracellular matrix proteins. *S. aureus*, the most common causative agent of septic arthritis, produces bacterial surface proteins that mediate adherence to extracellular matrix proteins and are known as "microbial surface components recognizing adhesive matrix molecules." Staphylococcal strains that are deficient in microbial surface components recognizing adhesive matrix molecules have been found to be less arthritogenic in animal models [32].

In septic arthritis patients, joint damage can be caused by bacterial invasion, host inflammation, and tissue ischemia. Bacterial enzymes and toxins cause direct damage to cartilaginous tissue. Cartilage may suffer "collateral" damage when host neutrophils release active oxygen species and lysosomal proteases. Cytokines activate host matrix metalloproteinases, resulting in the autodigestion of cartilaginous tissue. Ischemic injury also plays a role in this process. Cartilage is avascular and thus highly dependent on the diffusion of oxygen and nutrients from the synovium. When purulent exudates accumulate around a joint, pressure increases and synovial blood flow is compromised, resulting in cartilage anoxia [33]. Under these conditions, cartilage synthesis is inhibited, the degradation of cartilaginous tissue accelerates, and irreversible bone loss occurs [27], as shown by a case of septic arthritis of hip joint where a delayed presentation of more than 3 weeks predicted higher joint damage and led to the need for excision arthroplasty [34].

Clinical Features

Bacterial arthritis generally involves acute onset of localized pain, tenderness, swelling, and decreased range of joint motion. Gonococcal and nongonococcal arthritis produce characteristic signs and symptoms that can be easily used to make a diagnosis. Acute infectious arthritis is usually monoarticular but can easily overlap with other causes of polyarthralgia, mainly because monoarthritis is frequently the form in which polyarticular diseases present themselves. In patients with monoarthritis, a differential diagnosis should consider two other conditions: trauma and crystal-induced arthropathies [35]. In 80–90% of cases, only one joint is affected [36].

Nongonococcal arthritis usually appears in patients with a short history of high fever and leucocytosis. Most importantly, it manifests as a single, hot, swollen, and intensely painful joint, mainly one of the large ones, with more than 50% of cases involving a knee [37]. Approximately 20% of nongonococcal arthritis cases are polyarticular, affecting 2–3 large joints, although this is observed mainly in patients with chronic degenerative diseases such as rheumatoid arthritis and osteoarthritis [26, 35].

It is not easy to make a clinical and laboratory diagnosis of nongonococcal bacterial arthritis. Clinical manifestations such as high-grade fever are only present in 58% of the cases [4], even though low-grade fever may be present in approximately 90% of the patients; regarding leucocytosis, it is only found in 50% of the patients [38]. In patients with rheumatoid arthritis or in patients under treatment with corticosteroids or immunosuppressive drugs, joint pain may be masked, which can delay diagnosis.

Gonococcal infection is the most common cause of monoarthritis in sexually active young adults. The female to male ratio is 3:1, which might be explained by the fact that women are more frequently affected by asymptomatic, and thus untreated, genito-urinary tract infections [39–41]. Disseminated gonococcal infection affects 0.5–3% of patients with mucosal infection; these patients usually present severe polyarthritis that may resolve spontaneously [42]. This type of infection is associated with a characteristic triad of clinical components that includes migratory polyarthralgia; dermatological lesions, usually in the form of macules, papules, and tenosynovitis, the latter of which often affects multiple joints simultaneously (particularly wrists, fingers, ankles, and toes); and systemic inflammatory symptoms [43, 44].

This type of infectious arthritis usually presents in two forms, one as the classic triad defined above, also called arthritis dermatitis syndrome, and the other as a localized septic arthritis, an asymmetric polyarticular or monoarticular disease that appears in less than 50% of patients, usually affecting the knees, ankles, and wrists. Tenosynovitis usually affects wrists, ankles, and other small joints and is usually very painful; its most common dermatological features are non-painful macules or papules in arms or legs, although no specific location has been described [43].

Recent exposure to sexual activity should raise suspicion of the presence of this type of arthritis. Even though a positive gram stain of synovial fluid is found in less than 50% of the patients with this condition, cervical, urethral, and rectal cultures should be simultaneously obtained to increase the likelihood of a positive diagnosis, mainly by looking for the presence of *N. gonorrhoeae* [43]. Table 3.1 shows a summary of the clinical characteristics of gonococcal and nongonococcal arthritis.

Diagnosis

The methods to diagnose bacterial arthritis have not changed substantially in the last decades, and reaching a diagnosis continues to be challenging. The diagnosis is still mainly based on culturing and isolating the pathogen, and great

Table 3.1 Clinical characteristics of gonococcal and nongonococcal arthritis

Characteristics	Gonococcal	Nongonococcal
Patient profile	Young sexually active adults, mainly women	Newborns or chronic diseased adults (diabetes, RA, OA)
Presentation	Migratory polyarthritis Dermatitis, tenosynovitis	Single joint affectation
Joint affection	Polyarticular approx. 50%	Oligoarticular approx. 90%
Positive culture	Less than 50%	Nearly 90%
Prognosis	Good with adequate antibiotic therapy	Usually bad prognosis, requiring joint drainage in most cases

Modified from: Goldenberg [27]

Table 3.2 Clinical and laboratory data suggestive of infectious arthritis

Key clinical data	Joint fluid characteristics
Recent onset of fever, general malaise	More than 50,000 cells/mL
Arthralgia and synovitis (mono/polyarticular)	More than 90% polymorphonuclear cells
Risk factors for infectious arthritis	Positive gram stain and culture Low glucose and high lactate

Modified from Shirtliff and Mader [36]

emphasis is put on differentiating between the two major types of infectious arthritis, which is the subject of this review. It is generally agreed that gonococcal arthritis is one of the main causes of septic arthritis and that differentiating it from nongonococcal arthritis is of great importance due to the associated prognostic and outcome factors.

In most medical conditions, achieving an accurate diagnosis depends on a combination of clinical data, laboratory information, and radiological images. In the case of infectious arthritis, the diagnosis depends 100% on clinical and laboratory data as shown in Table 3.2.

A definite diagnosis of bacterial arthritis can be established only by visualizing the causative bacteria on a gram-stained smear or by culturing bacteria obtained from the synovial fluid by arthrocentesis. Gram stain and culture of synovial fluid should be obtained as a matter of routing in every case of undiagnosed arthritis, ideally before initiating treatment with antimicrobials. Gram staining of synovial fluid, however, is insensitive for the diagnosis of septic arthritis. Gram stains are positive in 71% of gram-positive cases of septic arthritis [4], in 40–50% of cases of gram-negative septic arthritis [45], and in less than 25% of cases of gonococcal septic arthritis [27]. Synovial fluid cultures are positive in 70–90% of cases of nongonococcal bacterial arthritis [27, 46]. Blood cultures are positive in 40–50% of cases of bacterial arthritis and are the only method of identifying the pathogen in about 10% of cases. Occasionally, an infection in an extra-articular site provides a clue to the etiologic agent infecting the joint. For example, bacterial arthritis is sometimes associated with pneumococcal pneumonia or with a urinary tract infection by *E. coli.*

In gonococcal infections, *N. gonorrhoeae* can be diagnosed by culture or nucleic acid amplification tests (NAATs), and sometimes by gram stain. Cultures of skin lesions are almost always negative, while less than 50% of synovial fluid cultures, and less than one third of blood cultures, are positive. This may be due to the difficulty of culturing these microorganisms. Tenosynovitis and dermatitis, which are associated with disseminated gonococcal infection, may not yield viable organisms; however, they can be easily recovered from the genitourinary tract. Synovial, skin, urethral, cervical, or rectal cultures on Thayer-Martin medium should be made in all cases of patients with clinical features of gonococcal arthritis. Around 50% of patients with gonococcal arthritis have positive cultures from one of the mucosal sites mentioned above [47]. If an associated urethritis is present, a gram stain of the urethral exudate should be collected and examined for the presence of gram-negative diplococci, which are characteristic of *N. gonorrhoeae* infection. Cultures and gram stains of specimens obtained from skin lesions or tendon sheaths are often negative. Due to their superior sensitivity and high specificity, nucleic acid amplification tests (NAATs) have in recent years rapidly replaced cultures as diagnostic tests. In a study of an Australian population with gonococcal arthritis, the most commonly used method to confirm infection was NAAT for *N. gonorrhoeae* in a joint aspirate, followed by urinary NAAT [48]. Ideally, NAATs would be combined with the targeted deferred culture of positive samples for monitoring antimicrobial resistance [49].

The organisms causing nongonococcal septic arthritis in adults are 75–80% gram-positive cocci and 15–20% gram-negative bacilli [4]. The most common organism in native and prosthetic joint infections is *S. aureus*. The next most common group of gram-positive aerobes found in prosthetic joint infections is *Streptococci*, which includes *S. pneumoniae.* The most frequently found groups, after *Streptococcus pyogenes*, are groups B, G, C, and F. Non-group A streptococcal disease is usually present in patients with immunosuppression, diabetes mellitus, malignancy, or severe genitourinary or gastrointestinal infections [50]. Group B streptococcal arthritis is only rarely present in adults; however, it should be considered a serious infection in patients with diabetes and in those with prosthetic hip infections [51]. Infections with gram-negative bacilli are usually found in patients with a history of intravenous drug abuse, in immunocompromised patients, and in very old patients [52]. The most common gram-negative organisms found in these patients are *E. coli* and *P. aeruginosa*.

Infections caused by anaerobes are detected in 5–7% of septic arthritis cases [21, 46]. Common anaerobes found in these patients include *Bacteroides, Propionibacterium acnes*, and various anaerobic gram-positive cocci. If foul-smelling synovial fluid or air is found in the joint space, anaerobic infection should be suspected, and appropriate cultures should be obtained and kept for at least 2 weeks. This type of infection is most frequent in immunocompromised patients, and in patients with wound infections or joint arthroplasty.

Polyarticular septic arthritis is much less common than the monoarticular variant [36]. Many patients with polyarticular septic arthritis have one or more comorbidities, and some have been intravenous drug abusers. The prevalence of this type of arthritis in patients with rheumatoid arthritis is high, with an average of 25% (ranging from 18% to 35%) [53]. Although *S. aureus* is the most frequently found pathogen in polyarticular infections, *G. streptococci, H. influenzae, S. pneumoniae*, and mixed aerobic and anaerobic bacteria have also been responsible for polyarticular infections.

Taking plain radiographs of infected joints is normal procedure at presentation, and they should be obtained in all such cases, given the possibility, although rare, of associated osteomyelitis or concurrent joint disease. Furthermore, a baseline radiograph is often useful for comparison purposes in cases where the patient's response to therapy is delayed or poor. Radiographs often show nonspecific alterations caused by inflammatory arthritis, including periarticular osteopenia, joint effusion, soft tissue swelling, and joint space loss. Scintigraphy, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can detect effusions and inflammation in joints that are difficult to examine otherwise, especially in hip and sacroiliac joints, and the images thus obtained can be used to determine the extent of the infection [54, 55]. MRI is highly sensitive for early detection of joint fluid and is superior to CT delineation of soft tissue structures. MRI images can show early bone erosion, reveal the presence of soft tissue extension, and help in the arthrocentesis of shoulder, hips, acromioclavicular, sternoclavicular, and sacroiliac joints [56].

Treatment

Treatment of bacterial arthritis must begin immediately after the clinical evaluation has been done and appropriate cultures have been taken. Hospitalization and consultation with an infectious disease specialist are recommended for initial therapy. In patients with infectious arthritis, a good prognosis depends on the intensity of the initial treatment and choosing the correct antibiotics. The most commonly used therapy for this kind of patients consists of parenteral antibiotics during the acute phase of the disease and adequate joint drainage. The initial antibiotic therapy should always be broad spectrum until a particular pathogen is isolated and a specific antibiotic can thus be selected.

The use of antibiotics will depend on the local epidemiology, the clinician experience, and local hospital conditions such as the availability of medicines, especially in developing countries. A suitable antibiotic treatment must account for the geographic variations of organisms and their resistance patterns. Gram stain results and the assessment of the risk factors associated with the disease should guide the therapeutic regimen. Most antibiotics show good penetration into diseased joints. The use of parenteral antibiotics should last approximately 15–21 days, and PO antibiotics should be used afterward for a complete 4-week regime.

The most common therapeutic regimens use third generation cephalosporins with good outcomes, especially when the presence of *S. aureus* or *Streptococci* is highly suspected [57]. B-lactam, aminoglycosides, or quinolones are usually a good choice for gram-negative rods, but recently *N. gonorrhoeae* has shown an increasing resistance against quinolones, and this has led the CDC to discard their use as a viable therapy [58, 59].

Cefixime could be used as oral treatment after a course of intravenous cephalosporins, except against *Chlamydia*, which is resistant to cefixime [47]. Osteomyelitis is a feared outcome in all cases, especially when the infected joint is a cartilaginous one (sternoclavicular or sacroiliac); in those cases, treatment can last up to 6 weeks [60]. Table 3.3 summarizes the empiric antibiotic therapies that have been proposed.

Joint drainage has shown good results when combined with antibiotics, mainly because it improves the circulatory properties of the affected joint, decompresses it, and removes the offending microorganisms and their associated cascade of reactions. Whether arthrocentesis should be preferred over open surgery is still controversial. The known data suggest that arthrocentesis is more effective than open drainage, but the selection of surveyed patients was biased, and ill patients are certainly not good candidates for surgical procedures [37, 61]. There is no consensus about the effect of mobilization in patients suffering bacterial arthritis, but it has been suggested by several authors that early rehabilitation and mobilization yields better outcomes than immobilization,

Table 3.3 Proposals for empiric antibiotic use in bacterial arthritis

Gram stain of synovial fluid	Antibiotic therapy
Gram-positive cocci	Cefazolin 2 g IV q 8 h Cefotaxime 1 g IV q 8 h
Gram-negative cocci	Ceftriaxone 1 g IV q 24 h
Gram-negative rods	Cefepime 2 g IV q 8 h Piperacillin-tazobactam 4.5 g IV q 6 h
MRSA suspicion or risk factors	Vancomycin 1 g IV q 12 h

Modified from Ross [60]

especially with regard to preventing muscle atrophy and joint contractures [62].

Prognosis

Diagnosing and treating an infected joint as soon as possible is the key to a good prognosis. Septic arthritis is a life-threatening emergency with a high mortality (up to 11%). Almost half of the patients with infectious arthritis suffer permanent joint damage. The outcome is closely related to multiple factors, mainly comorbid conditions (e.g., immunocompromised conditions, osteoarthritis, and rheumatoid arthritis, as well as previous joint damage), but also pathogen virulence factors. All clinicians should be aware that an infectious process in a joint can be a potential cause of acute arthritis and should implement proper screening procedures to diagnose and treat it promptly.

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Septic Arthritis in Children: Clinical Update

4

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Introduction

Septic arthritis is commonly encountered in children and results from a purulent inflammatory response to a bacterial infection, most commonly *Staphylococcus aureus*. The most common mode of transmission is hematogenous dissemination to the synovial joint. Septic arthritis of the hip joints is a medical emergency, needing prompt diagnoses, drainage of the synovial space, and antimicrobial therapy to prevent poor outcomes [1]. The purpose of this chapter is to provide an overview of the etiology, microbiology, epidemiology, pathogenesis, approach to diagnosis, and treatment of septic arthritis in children.

Etiology/Microbiology

The microorganisms causing infectious arthritis include most commonly bacteria, followed by viruses and fungal organisms. Bacterial causes of pyogenic arthritis vary with age, immunization status, and certain predisposing risk factors and/or medical conditions such as immunosuppressive states or hemoglobinopathies. In the neonatal age group up to 2 months of age, the most frequently isolated organisms are *Staphylococcus aureus* and *Streptococcus agalactiae* (known as group B streptococcus) followed by enteric gram-negative organisms (*Enterobacteriaceae*) and *Streptococcus pneumoniae* [2, 3]. Other rare but important organisms in the neonates are *Salmonella* spp., *Neisseria gonorrhoeae*,*Candida albicans*, and the emerging *Candida* non-albicans species [4–7]. One notable non-albicans species is *C. parapsilosis*, with increasing prevalence over the past two decades and which is the second most commonly reported cause of systemic candidiasis in a cohort of neonates weighing less than 1000 g at birth (extremely low-birth-weight neonates) [8–10]. Past the neonatal age, infections with enteric gram-negative bacteria are rare in the pediatric population; nonetheless, they can be observed in association with direct inoculation by intravenous drug use (IDU), surgical instrumentation, and trauma and in hosts that are immunocompromised [5].

Pseudomonas aeruginosa has been associated with septic arthritis in infants at sites of puncture wounds and in adolescents with IDU and following nail injuries through a sneaker [11–13]. In infants and young children up to 59 months of age, *Haemophilus influenzae* type b (Hib) was the most frequent bacterium isolated in pyogenic arthritis; however, with the implementation of the Hib vaccine for children in 1987 and infants in 1990, the incidence of typeable invasive *H. influenzae* has dramatically decreased [14–16]. With this decrease in invasive Hib, *Staphylococcus aureus* has predominated as the most common etiologic cause of septic arthritis in all age groups [14, 17]. In children younger than 5 years of age, methicillin-susceptible *S. aureus* (MSSA), community-associated methicillin-resistant *S. aureus* (MRSA), *Kingella kingae*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* are common causes of pyogenic arthritis [3]. Although *S. aureus* continues to be the most common pathogen isolated from osteoarticular infections in children, *Kingella kingae* is being reported more frequently in the United States [18–21]. In a retrospective case series from 1999 to 2002, *Kingella kingae* was the most isolated organism in children under 36 months of age with a statistically significant value (p: 0.0003) [22]. In another series from Israel, *Kingella kingae* was the primary cause of septic arthritis in patients younger than 24 months of age, found in 48% of cases [23]. A rise in the diagnosis of *Kingella kingae*

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_4

osteoarticular infections is attributable to improvements in culture methods, growing best in aerobic conditions with carbon dioxide, and utilization of real-time polymerase chain reaction (PCR) [18, 24, 25].

Emphasis to underlying medical condition and immunosuppressed state must be considered as certain conditions predispose to certain bacteria. For instance, in the patient with sickle cell anemia, *Salmonella* spp. is a common cause of septic arthritis; however, atypical osteomyelitis and concurrent septic arthritis due to *Salmonella typhi* have been documented in normal hosts [26]. Patients with malignancy and immunosuppression can present with septic arthritis due to *Aeromonas* spp., *Enterobacter* spp., *Serratia* spp., *Bacteroides* spp., *Pseudomonas* spp., *and Campylobacter* spp. [13, 27].

The exposure history must be considered in evaluating for possible bacterial etiologies of septic arthritis. If clinical findings of septic arthritis arise after an animal bite, multiple organisms must be considered depending on the animal. Bites by cats, dogs, or mammals have multiple organisms that can be pathogenic including *Pasteurella* spp., *Staphylococcus aureus*, *Streptococcus* spp., *Capnocytophaga* spp., *Moraxella* spp., *Corynebacterium* spp., and *Neisseria* spp. [28]. In cases of cat or dog scratches or bites, *Bartonella henselae*, etiology of cat-scratch disease, has to be in the differential as a rare cause of septic arthritis. For reptile bites, enteric gram-negative bacteria and anaerobes are considered. For human bites those considered include *Streptococci* spp., *S. aureus*, *Eikenella corrodens*, *Haemophilus* spp., and anaerobes. In rat bites a disease known as rat-bite fever can rarely present with septic arthritis and is attributable to *Streptobacillus moniliformis* and *Spirillum minus* [29]. It is important to recognize rat-bite fever as the case fatality rate is 7–13% in patients that do not receive therapy [29]. Another exposure history to consider is tick bites or finding of the characteristic rash of erythema migrans in endemic areas as a cause of Lyme arthritis secondary to *Borrelia burgdorferi*; refer to the chapter on Lyme arthritis for further details. A detailed travel history and exposure history including consumption of raw food and unpasteurized milk or cheese must be inquired as they can be associated with septic arthritis *caused by Brucella* spp. [3, 5].

Unusual organisms reported to cause pyogenic arthritis in children include *Actinomyces pyogenes*, *Propionibacterium acnes*, and *Pasteurella multocida* [13, 30–32]. Chronic monoarticular septic arthritis can arise due to brucellosis, *Mycobacterium tuberculosis* or non-tuberculosis mycobacterium, *Candida* spp. (seen in intravenous drug users), and *Nocardia asteroides* [12, 13]. Besides *Candida* spp., other fungal infections have been attributed to septic arthritis, and travel history or having lived in an endemic area for a dimorphic fungus has to be elicited. Dimorphic fungi known to cause septic arthritis by dissemination are *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Sporothrix schenckii* [33–36]. Viral etiologies are less likely to cause infectious arthritis in comparison to bacterial etiologies. The most common viruses include parvovirus B19, rubella virus, arboviruses (dengue, chikungunya), and hepatitis B [3]. Other less common viruses include varicella-zoster virus, enterovirus, Epstein-Barr virus, mumps virus, cytomegalovirus, and human immunodeficiency virus [3, 13].

Epidemiology

The incidence of septic arthritis is more common in children; the estimated incidence is 1–37 cases per 100,000 people, with a male-to-female predominance of approximately 2:1 [37, 38]. In a Norwegian prospective population-based, multicenter study from 2004 to 2005, children under 16 years old suspected of having arthritis were referred to the local department of pediatrics or rheumatology. The incidence of arthritis was 71 per 100,000 children, septic arthritis was found in 5 per 100,000 children, and the incidence was higher in children younger than 8 years old with a male predominance [37]. The epidemiology observed in the Norwegian study is similar to multiple case series, highlighting that most cases occur in children younger than 6 years of age, that peak incidence occurs in children younger than 3 years old, and that boys are affected twice as more compared to females [14, 17, 37, 39–43]. A history of trauma may precede the development of pyogenic arthritis and is temporally associated with acquisition by *Staphylococcus aureus*; however, eliciting a history of trauma is less common in septic arthritis in comparison to osteomyelitis [14, 44–46]. A preceding history of an upper respiratory infection often precedes pyogenic arthritis that is caused by HiB and *Kingella kingae*. Both *Kingella kingae* and HiB can colonize the human posterior pharynx [25]. With an upper respiratory infection, the oral pharyngeal mucosa is damaged which predisposes the colonized microorganisms to spread to the blood. Bacteremia occurs with potential hematogenous spread to the synovial fluid (explained in more detail in the pathophysiology section). In the case of *Kingella kingae*, gastroenteritis, aphthous stomatitis, or an upper respiratory infection can increase the likelihood of transient bacteremia due to mild traumatic injuries to the mucosa and often precede septic arthritis by hematogenous spread to the affected joint [14, 19, 25, 40, 47–49]. Outbreaks of child-to-child transmission have been reported in child care centers resulting in osteoarticular infections [50, 51]. In children younger than 4 years of age, *Kingella kingae* has replaced *H. influenzae* as the main pathogen of gram-negative hematogenous pyogenic arthritis [19, 23, 47, 49]. Overall, many children do not have an underlying risk factor for septic arthritis; nonetheless, risk factors that predispose to septic arthritis include immunodeficiency, hemoglobinopathy, recurrent

hemarthrosis, diabetes, intravenous drug use, and rheumatoid arthritis. Extra-articular spread of infection for septic arthritis, other than osteomyelitis in 9–33%, does not frequently occur in the modern age of antibiotic use [13, 52–55].

Pathogenesis

Septic arthritis is caused by various mechanisms. The most commonly observed mode of acquiring pyogenic arthritis in children is by direct seeding of bacteria by hematogenous spread to the synovial membrane [56]. Other mechanisms include direct inoculation by trauma or surgical infection and from spread from a contiguous focus of infection (as seen with osteomyelitis). The synovial joints are composed of synovia (transparent synovial fluid which is viscous with hyaluronic acid and IgG) [44]. The synovium, also known as the synovial membrane, is embarked with the formation of synovia. The synovial membrane is a highly vascularized region with a vast capillary supply that functions to nourish, lubricate, and cushion the avascular cartilage of the joints [44]. Noticeably, the synovium has a rich blood supply and lacks a barrier basement membrane, making it prone to hematogenous spread and seeding to the synovial space [10, 44]. Children, particularly younger than 18 months, have increased vasculature connecting the metaphysis and epiphysis, termed transphyseal blood vessels, allowing contiguous spread from a primary metaphyseal osteomyelitis into the joint space through the epiphyseal growth plates or vice versa with the spread to the metaphyseal bone from the infected synovium [57, 58]. The extension from a primary septic arthritis of the hip or shoulder to a secondary osteomyelitis of the femur or humerus most notably occurs in neonates and in children with *K. kingae* [3, 55]. Septic arthritis may also occur through direct inoculation of a pathogen into the sterile joint space by surgical procedures such as arthroscopy, prosthetic joint implantation or revisions, intra-articular injection of corticosteroids or other medications, and penetrating trauma to the joint space [44, 59–61].

The pathophysiology of septic arthritis consists of adherence of the organism to the synovial membrane and bacterial proliferation in the synovial fluid that results in an inflammatory response [62]. Various experimental animal models have been studied to further comprehend the pathogenesis of septic arthritis. The synovial fluid inhibits growth of bacteria in vitro; however, *Staphylococcus aureus*, one of the bacteria most studied in the pathogenesis of septic arthritis, has developed methods of resistance to overcome the defense mechanism of the synovial fluid. *Staphylococcus aureus* adheres to the bone matrix (laminin, fibronectin, collagen, and bone sialoglycoprotein) by bacterial adhesins or microbial surface components that recognize matrix molecules (MSCRAMMs) [44, 63–67]. The strains of *Staphylococcus aureus* lacking the genes encoding MSCRAMMs are less likely to result in osteoarticular infection in animal models [64, 66–68]. Once the bacteria enter and adhere to the joint space, virulence factors, such as formylated peptides, mediate the recruitment of neutrophils [69]. Neutrophils are essential in bacterial clearance but also contribute to tissue damage via enzyme release and free radical formation [67]. Bacterial exotoxins recruit T cells and activated macrophages to the joint space, resulting in the release of an inflammatory cytokine cascade. Cytokines released include gamma interferon, tumor necrosis factor, interleukin 1, interleukin 2, interleukin 6, and interleukin 7 [67, 70]. These cytokines stimulate the release of proteolytic enzymes by the cells in the synovial lining and chondrocytes that enhance leukocyte migration and also promote increased intra-articular pressure [44]. This increase in pressure by accumulation of purulent synovial fluid leads to ischemia and destruction of the synovium and cartilage [44, 56]. It is the host's inflammatory response to a pathogen that leads to most of the damage to the joint as early as 3 days [71, 72].

Clinical Manifestations

Septic arthritis initially presents with systemic manifestations of fever, irritability, or decreased appetite. Neonates or infants present with nonspecific symptoms of hyperthermia or hypothermia, decreased activity, decreased appetite, desaturations, lethargy, irritability, and/or pseudoparalysis of the extremity involved. Subtle signs and symptoms, such as fever, can be absent in a neonate with septic arthritis; thus, a high index of suspicion has to remain in this vulnerable population [44]. The hip and knee joints are most commonly affected in neonates [73, 74]. More localized findings are observed in older children such as pain in the involved joint progressing to edema and rubor of the overlying skin. Septic arthritis presents in a monoarticular fashion in more than 90% of cases [40]; however, polyarticular presentations can occur with *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Salmonella* spp. [3]. The weight-bearing joints of the lower extremities are affected in approximately 75% of cases, with the knee being most commonly affected followed by the hip and ankle [40, 75]. The elbow and shoulder can also be affected with less frequency [48]. When the upper extremity is affected, pseudoparalysis of the affected joint can be seen with associated point tenderness on palpation and decreased range of passive or active motion with associated pain [3]. In the infant population, the hip is also one of the most affected joints; interestingly, rubor and edema may not be present which makes it difficult to diagnose [3, 13]. Overall, the smaller distal joints are less affected in comparison to the proximal larger joints [44].

Physical examination and clinical findings vary with the age group affected. In general, focal joint tenderness can be

elicited with erythema of the overlying skin and effusion or edema. Passive joint movements increase intracapsular pressure causing pain and decreased range of motion. The neonate and infant with hip involvement may cry or become irritable with diaper changes or when the joint is moved [3]. Diminished movement of the affected limb is often observed, temporally unrelated to birth trauma [74, 76]. On further evaluation, tissue edema around the hip joint can be seen, often encompassing the entire leg [3]. An infant or child with septic arthritis of the hip is seen to lie with the affected leg held in a flexed, externally rotated, abducted position, resisting passive range of motion [77]. The affected joint can dislocate due to the edema and buildup of pressure [77]. Older children with pyogenic arthritis of the hip often complain of pain, especially when weight bearing or when the head of the femur is compressed into the acetabulum. The hip pain can be associated with referred pain to the knee [77].

Neonates are a special population in which osteomyelitis and septic arthritis often occur concomitantly [44]. They have an increased vascular supply connecting the metaphysis blood vessels directly through the physis and into the epiphysis [44, 78]. This direct blood supply predisposes neonates to contiguous spread of pathogens to the epiphyseal end of the bones resulting in a concomitant osteomyelitis [57]. Vigilance is needed in patients with central line-associated bloodstream infections, with attention to premature neonates and immunosuppressed populations, as hematogenous spread of pathogens (such as MSSA, MRSA, and coagulase-negative staphylococci) to distant sites can result in osteomyelitis and septic arthritis as part of disseminated disease [79, 80].

Diagnostic Evaluation

A clinical suspicion of septic arthritis is based on history and physical exam that should lead to a laboratory, radiographic, and surgical intervention for therapeutic and diagnostic reasons. Evaluation of the joint fluid is essential as the identification of the organism establishes a diagnosis. Initial laboratory evaluation includes a serum complete blood count and differential looking for leukocytosis and neutrophil predominance, erythrocyte sedimentation rate (ESR), C-reactive protein, blood culture, and PCR analysis of synovial fluid looking for *K. kingae* or other fastidious-growing organisms in the pertinent patient population.

Laboratory and Joint Fluid Findings

The laboratory evaluation of pyogenic arthritis often shows peripheral leukocytosis with neutrophil predominance and acute-phase reactants such as elevated erythrocyte sedimentation rate (ESR) with values more than 20 mm/h and elevated C-reactive protein (CRP) with a mean value of 8.5 mg/dL [3, 81–83]. These tests are nonspecific for septic arthritis as they can be elevated with any infectious/inflammatory process and must be used as supportive evidence of septic arthritis in the right clinical context. Sensitivity for the diagnosis of osteoarticular infections increases with the combination of an elevated CRP and ESR; however, children with osteoarticular infections with *K. kingea* frequently do not have elevated inflammatory markers [3, 83, 84]. The ESR is a nonspecific value of inflammation that reflects concentrations of fibrinogen and immunoglobulins in the plasma [44]. ESR rises in 24 h after the onset of an inflammatory trigger, slower than C-reactive protein, slowly returning to normal in approximately 4 weeks [44, 85]. The CRP is a better positive predictor of septic arthritis in comparison to ESR with a positive predictive value ranging from 34% to 53%. However, CRP is better utilized as a negative predictor value for septic arthritis ranging from 78% to 87% in CRP values <1.0 mg/dl [86]. Serum procalcitonin (PCT) is also an acute-phase reactant that is being evaluated as a diagnostic marker for septic arthritis. In a meta-analysis in adults, PCT was more sensitive and specific in comparison with ESR and CRP for the diagnosis of osteoarticular infections. In patients with septic arthritis, the sensitivity was 55% and specificity 88%, thus suggesting that PCT can be used to rule in infection rather than for exclusion of osteoarticular infections [87]. Studies are needed in the pediatric population to further evaluate the utility of PCT in osteoarticular infections. CRP is often used, in conjunction with other laboratory data, to follow early response to antibiotic therapy and overall clinical progression [44, 83, 88]. CRP peaks in 48 h, and in uncomplicated cases with proper antibiotic coverage, it can normalize within 1 week [78]. A rise in CRP in a patient who is clinically decompensating is concerning for recrudescence of a primary infectious process and suboptimal source control of pyogenic arthritis [44, 89].

The synovial fluid of the affected joint must be collected in a heparinized syringe to prevent clot formation and optimize the enumeration of leukocytes [13]. The synovial fluid is usually observed to be turbid and purulent [44]. It should be analyzed using a Gram stain, aerobic and anaerobic culture, and cell and differential count. A leukocyte count greater than 50,000 cell/mm^3 with predominance of polymorphonuclear neutrophils is suggestive of a septic arthritis; nonetheless, counts greater than 50,000 cells/mm^3 can occur in juvenile rheumatoid arthritis or Lyme disease, and lower WBC counts do not necessarily exclude a diagnosis of septic arthritis [44, 52, 56, 90–93]. Table 4.1 depicts the synovial fluid characteristics in various types of infectious arthritis. Synovial fluid glucose may be low and protein and lactate dehydrogenase may be elevated; however, these tests have low sensitivity and specificity, not allowing for a reliable differentiation of infectious and inflammatory pro-

Table 4.1 Synovial fluid findings in infectious arthritis

Diagnosis	White blood cells/mm^3	% polymorphonuclear leukocytes	Glucose (median, mg/dL)
Normal	<200	<25	____
Pyogenic arthritis	40,000–300,000	>90	30
Candida arthritis	10,000–220,000	>90	60
Juvenile rheumatoid arthritis	15,000–20,000	60–75	75
Reactive arthritis	20,000–40,000	50–75	_____
Tuberculous arthritis	40–136,000	>50	_____
Lyme arthritis	180–140,000	>75	_____
Viral arthritis	3000–50,000	<50	_____

Data from references [44, 92, 154, 155]

cesses [44, 94]. In patients who have not previously received antibiotics, the yield of a bacterial organism from joint culture is 60% to 70%, but some studies have reported culture positive rates up to 80–90% [40, 95–98]. To increase the yield of certain fastidious pathogens from joint cultures such as *K. kingae*, it is recommended to have direct inoculation of the synovial fluid into pediatric blood culture media bottles [20, 99].

A limitation of the Gram stain is that it stains in only 50% of positive cultures, but it is still useful since approximately 35% of joint aspirates can have no growth on culture [14, 95]. Gram stains must be evaluated with caution as false-positive results can occur from artifacts in staining or in patients with previous antibiotic administration due to increased cellular debris and/or presence of mucin [100]. It is important to obtain blood cultures and synovial cultures before the initiation of antibiotics to increase the yield of isolating an organism, unless the patient has signs of sepsis. In negative synovial cultures, blood cultures are the only source of isolating an organism in approximately 10% of cases of septic arthritis [100]. Blood culture positivity varies from different studies, ranging from 25 to 70% in adults to approximately 40% in children [56, 96, 99].

An emerging technology since the 1990s is the use of polymerase chain reaction (PCR) in the identification of fastidious pathogens [13]. Real-time polymerase chain reaction (RT-PCR) assay uses specific primers that amplify the genes of bacteria. This targeted approach has increased the yield of pathogens [101–103] by increasing the sensitivity with a faster time to detection without significantly decreasing specificity in comparison to PCR methodologies that use broad-range 16 sRNA primers [13, 103–107]. In a review, the isolation of *K. kingae*, which is a common cause of septic arthritis in children younger than 5 years old, was analyzed using synovial fluid inoculated in blood cultures yielding 29% positivity; with conventional methods of PCR, the yield increased to 41%, and with RT-PCR the yield increased further to 49% [108]. A great advantage of PCR is that rapid results are obtained, and there is a higher likelihood of isolating a pathogen in patients that have been pretreated with antibiotics [100]. Limitations of PCR are that it may not be available in many microbiology laboratories, false-positive results often occur due to sample contamination, and it is unable to provide susceptibilities [103]. Recent advances in diagnosis include the use of matrix-assisted laser desorption/ionization time-of-flight-mass spectrometry (MALDI-TOF MS) which can rapidly identify bacteria at the subgroup level within a species once bacteria grow in agar media [109, 110].

Imaging

In the early presentation of septic arthritis in children, plain radiographs outside the neonatal age group are often normal [111]. Periarticular soft tissue swelling and widening of the joint space secondary to joint effusions can be seen [44, 78]. Early radiographic findings are capsular swelling with obliteration or lateral displacement of gluteal fat lines and asymmetric fullness of the obturator internus and iliopsoas soft tissue planes [112]. As pressure builds up in the joint capsule, especially the hip, the femoral head is displaced upward and outward, resulting in lateral subluxation. The lateral subluxation of the septic hip is particularly seen via plain radiographs in neonates and infants [111]. Erosion of the subchondral bone may be seen 2–4 weeks after the onset of acute infection [112]. The onset of avascular necrosis is evident by the appearance of sclerosis and decreased volume in the proximal femoral epiphysis [44, 78, 113].

In children the plain radiograph can be normal, and a better radiologic modality such as an ultrasound is needed to diagnose septic arthritis of the hip [111]. The best modality to detect early septic arthritis of the hip is ultrasonography since, if performed correctly, it can detect small intra-articular fluid collections [114]. Once fluid is detected in the hip joint, a diagnostic aspiration via arthrocentesis should be performed, without having to perform more advanced imaging, for cell count and cultures and to establish the diagnosis [1, 44, 78, 115]. Keep in mind that false-negative ultrasonography results can occur in the evaluation of septic arthritis within 24 h after the onset of symptoms; therefore, it is imperative to obtain blood cultures, CBC with differential, CRP, and ESR to guide management and to repeat ultrasonography in cases still concerning for septic arthritis or when bilateral disease of the hip occurs [116].

Scintigraphy, including technetium phosphate radionuclide scanning, is not typically used for the diagnosis of pyogenic

arthritis since it is a sensitive but nonspecific indicator of an osteoarticular infection [117]; nonetheless, it can be used in a nonverbal child or children with ongoing bacteremia to evaluate for another potential focus of infection as multifocal septic arthritis and/or osteomyelitis [113]. Scintigraphy studies in septic arthritis are characterized by an increased uptake in the early "blood-pool" phase and delayed images of the joint [44, 78]. The increased bony uptake is observed in symmetric sides of the joint, which differentiates it from osteomyelitis [3, 44, 78, 111]. Computed tomography (CT) is often used to evaluate deep articulations with complex anatomy and fibrocartilaginous articular structures such as the pubic symphysis, hip, sacroiliac joints, and sternoclavicular joints. CT detects erosive changes to the bone and joint effusions [3, 100, 117–121]. It is frequently used in the evaluation of intravenous drug users with concerns of septic arthritis due to *Pseudomonas aeruginosa*, as this pathogen has an affinity for the fibrocartilaginous structures mentioned. The modality of choice to diagnose septic arthritis is magnetic resonance imaging (MRI), being more sensitive than CT in delineating soft tissue structures and abnormalities of adjacent bone [3, 44, 100, 122]. Some authors advocate for an MRI as the initial evaluation of septic arthritis of the shoulder or elbow due to the high rates of concomitant osteomyelitis given the delay in presentation and complicated disease course [13, 123–126]. In general, MRI has more specificity in comparison to scintigraphy or CT and has replaced them as the modality of choice for the evaluation of osteoarticular infections [127, 128].

Management

In children suspected of having septic arthritis, a multidisciplinary approach is needed including rheumatology and/or orthopedics for prompt assistance with diagnostic arthrocentesis [100]. Orthopedic consultation is necessary for surgical drainage via arthrotomy, arthrocentesis, or open surgical drainage, allowing for drainage, irrigation, and debridement [42, 45]. Pediatric infectious disease doctors provide input for recommendations on empiric antibiotic options, and long-term follow-up is imperative at the initial presentation. A rapid diagnostic evaluation is needed, especially in septic arthritis of the hip in children, as it is an emergency and warrants prompt surgical drainage and irrigation of the joint space with appropriate antibiotic therapy in the first 6–12 h from presentation to decrease long-term associated morbidity [1, 42, 45].

Surgical Treatment

The goal of surgical intervention includes decompression of the joint, sterilization of the joint, and removal of inflammatory debris to prevent articular damage and preserve joint function [3, 129]. Surgical options for drainage include arthroscopy and open arthrotomy, allowing for direct visualization, irrigation, lysis of any adhesions, and removal of purulent material [100, 129–131]. In joints other than the hip, single or multiple needle aspirations may be an option to surgical drainage and are often individualized on clinical progress; however, surgical drainage is recommended when multiple needle aspirations fail to control the infectious process [3, 64, 91, 98, 100, 132–135]. In the case of septic arthritis of the hip, open surgical drainage should be performed immediately [44, 64, 78, 91, 98, 133–137]. To date, a controlled, prospective, randomized trial has not been done to evaluate the multiple surgical procedures [44, 45, 78, 113]. A retrospective study in adults evaluated the outcome of septic arthritis in patients treated by surgical drainage in comparison to repeat needle aspirations. The results showed equivalent results in arthritis of the knee, but overall, repeat aspirations were found to be superior to surgical drainage [44, 78, 138]. Multiple factors influence the modality of drainage such as availability of resources, joint involved, and clinical presentation [100]. Needle aspiration may be considered if the joint is accessible and has high probability of adequate drainage and the patient lacks poor prognostic factors such as neurovascular compromise, sepsis, prolonged duration of symptoms prior to evaluation, and significant comorbidities [64, 98, 100, 134]. In children, there are well-established indications for surgical drainage which include the following: involvement of the hip joint with some authors considering the shoulder as it often has delayed presentation and complicated disease course; presence of bacterial inoculum seen as large amounts of pus, debris, and fibrin or loculation within the joint space; and lack of clinical improvement within 3 days of appropriate antibiotic therapy [44, 67, 78, 95, 126, 132, 139].

Antimicrobial Therapy

A determination of empiric antibiotic choices to target the most common pathogens is based on the patient's age, risk factors, clinical presentation, and physical examination. Antibiotic selection is based on the identification of an organism, susceptibility profile, high synovial fluid-to-serum concentration ratios to guarantee penetration into the joint, and side effect profile [3]. The antibiotics used in septic arthritis achieve penetration into the joint; therefore, there is no indication for intra-articular instillation [3]. As discussed, an appropriate diagnostic evaluation including blood cultures, synovial cultures, and/or PCR evaluation of synovial fluid is needed to attempt to identify a microorganism and appropriately tailor antibiotics based on susceptibilities. In cases where a microorganism is not isolated, the patient is continued on empiric treatment based on the most common pathogen for age and mode of acquisition. Refer to Table 4.2

Table 4.2 Empiric antibiotic treatment of pyogenic arthritis in children with no immunosuppression

Age group	Likely pathogens	Antibiotics[a]
Neonates (<28 days of age)	*Staphylococcus aureus*[b,c] *Streptococcus agalactiae (GBS)* Gram-negative bacilli *Neisseria gonorrhoeae* (consider)	Nafcillin or clindamycin or vancomycin[b,c] + Ampicillin + gentamicin or cefotaxime
Children 3 months–5 years of age	*S. aureus*[b,c] *Kingella kingae* *Haemophilus influenzae* *Streptococcus pyogenes* *Streptococcus pneumoniae*	Nafcillin or clindamycin or cefazolin or vancomycin[b,c] + Cefotaxime or ceftriaxone
Children >5 years of age	*S. aureus*[b,c] *Streptococcus pyogenes*	Nafcillin or clindamycin or cefazolin or vancomycin[b,c]
Adolescents	*S. aureus*[b,c] *Neisseria gonorrhoeae* (consider)	Nafcillin or clindamycin or cefazolin or vancomycin[b,c] + Ceftriaxone

[a]For dosing recommendations, refer to the 2018–2021 *Red Book: Report of the Committee on Infectious Diseases*, 31st edition (Tables of Antibacterial Drug Dosages, pages 914–932) [140]

[b]If more than 10% of community-acquired isolates are MRSA, consider empiric therapy with vancomycin or clindamycin. If 10–20% of MRSA isolates are resistant to clindamycin, consider empiric therapy with vancomycin

[c]In isolates that are MSSA, the antibiotic of choice is nafcillin or cefazolin. Keep in mind that clindamycin MSSA resistance is increasing

for empiric antibiotic therapy based on the age group and specific therapy of choice based on the microorganism isolated. For recommended doses of neonates and children, refer to the 2018–2021 *Red Book: Report of the Committee on Infectious Diseases*, 31st edition (Tables of Antibacterial Drug Dosages) [140]. All cases of septic arthritis with or without concomitant osteomyelitis should initially receive parenteral therapy to ensure adequate serum concentrations and penetration into the affected site.

Regardless of age, all patients should receive an empiric antibiotic regimen with activity against *Staphylococcus aureus* as it is the most common cause of septic arthritis. Many experts advocate for empiric use of vancomycin or clindamycin against community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) when resistant rates to methicillin are greater than 10% [141]. With the use of vancomycin, it is important to closely monitor serum creatinine as it is a nephrotoxic agent and to monitor trough levels for both therapeutic levels and for potential toxicity. In children, trough levels of 15–20 mg/L are acceptable for MIC values greater than 2 mg/L; however, many agree that lower trough levels of 10–15 mg/L are acceptable in children when an MIC value is equal or lower to 1 mg/L as the area under the curve (AUC)/MIC achieved is greater than 400 mg∗h/L. AUC/MIC levels greater than 400 mg∗h/L are associated with early response to vancomycin in MRSA bacteremia [142]. It is important to note that many MRSA strains are acquiring clindamycin-inducible resistance; some advocate to use vancomycin as empiric therapy when clindamycin resistance is greater than 10–20% or when the patient has concomitant MRSA bacteremia or in sepsis. The decision to deescalate to clindamycin from vancomycin can be made once it is confirmed that there is no inducible resistance and the patient does not have MRSA bacteremia (clindamycin is not recommended to treat MRSA bacteremia). To verify if the MRSA strain exhibits clindamycin-inducible resistance, a D-test must be performed by the microbiology department. Other alternatives for MRSA coverage include linezolid and daptomycin which are used when a patient is failing therapy with vancomycin and/or when vancomycin has intermediate resistance and the patient is not clinically responding 3–5 days into vancomycin therapy (vancomycin intermediate resistance is seen when the vancomycin MIC to *Staphylococcus aureus* is 2 ug/ml) or when a patient has a drug allergy to vancomycin [100]. If daptomycin is used, a baseline creatinine kinase needs to be obtained and monitored throughout therapy. Daptomycin is only available in parenteral formulation, and no formal randomized study has been performed in pediatrics or adults for daptomycin use in native joint septic arthritis. Linezolid has been used in some instances of severe MRSA infection. It has an oral formulation with equivalent bioavailability to the parenteral formulation; however, the side effect and drug adverse event profile of bone marrow suppression (leukopenia, anemia, thrombocytopenia), lactic acidosis after 2–3 weeks of therapy, optic neuropathy, and nonreversible peripheral neuropathy limits long-term use [3, 100]. For isolates that are methicillin-susceptible *Staphylococcus aureus* (MSSA), therapy should be narrowed to a penicillinase-resistant penicillin such as oxacillin or nafcillin or cefazolin (first-generation cephalosporins) [100]. MSSA strains may be resistant to clindamycin. Ceftriaxone does have in vitro MSSA activity, but it is intrinsically less active than cefazolin and is not advocated for use in infections due to MSSA [100].

Empiric antimicrobial therapy in infants younger than 3 months of age should include activity against *S. aureus*, *Streptococcus agalactiae* (also known as group B streptococcus, GBS), and gram-negative organisms [3]. In both neonates and sexually active adolescents suspected of having septic arthritis secondary to *Neisseria gonorrhoeae*, ceftriaxone or

cefotaxime should be started empirically [4]. A good empiric coverage for infants younger than 3 months of age is anti-staphylococcal antibiotics discussed above and cefotaxime for GBS and gram-negative coverage. In infants and children aged 3 months to 5 years, empiric coverage for *S. aureus*, *K. kingae*, *S. pneumoniae*, and *S. pyogenes* (group A streptococcus) is recommended. Appropriate empiric therapy for the 3 months to 5 years old age group must target *S. aureus* coverage previously discussed and include the addition of ceftriaxone for *K. kingae*, GAS, and *S. pneumoniae* coverage [143]. In patients younger than 2 years of age who have not been immunized or completed a full course of HiB immunization, empiric therapy against *H. influenzae* type B (Hib) with a second- or third-generation cephalosporin should be started [13]. Keep in mind that Hib infection is not common in immunized children, but other typeable or non-typeable *H. influenzae* can rarely cause septic arthritis in children [3, 144]. Children older than 5 years of age are treated empirically for *S. aureus* and streptococci [3]. Special populations, such as children that are in immunosuppressive states or with hemoglobinopathies, are prone to gram-negative coliform bacteria or other gram-negative organisms such as *Salmonella* spp. Broad-spectrum antibiotics are needed in immunocompromised populations (such as patients with cancer, neutropenia, etc.) to provide coverage against *S. aureus* and gram-negative pathogens (e.g., a third- or fourth-generation cephalosporin such as ceftazidime or cefepime) [44, 78]. Patients with IDU are at risk of septic arthritis in the fibrocartilaginous articular structures with *Pseudomonas aeruginosa*, and empiric coverage is necessary with ceftazidime, cefepime, piperacillin/tazobactam, or meropenem.

All children with septic arthritis are started on parenteral therapy. Transition to an appropriate oral antibiotic option that has good gastrointestinal absorption and bioavailability is considered when defervescence occurs, control of infection has been achieved (source control), physical findings (joint pain, edema, rubor, erythema) resolve, and markers of acute-phase reactants normalize or significantly improve. Patients are frequently transitioned from parenteral to oral antibiotic therapy within 1 week in uncomplicated cases, when clinical improvement is established, CRP normalizes, and adherence and clinical follow-up are ensured [3, 85, 145–148]. Joint symptom resolution and clearance of infection from a septic joint are proportional to the duration of symptoms before surgical drainage and initiation of the appropriate antibiotic [13, 149, 150]. Duration of therapy depends on the specific causative organism, clinical response and time to sterility of the joint from drainage/initiation of appropriate antibiotics, laboratory response, and potential for a concomitant osteomyelitis [3]. Many authors consider a total duration of 3–4 weeks of therapy in septic arthritis due to *S. aureus* or gram-negative enteric organisms due to the frequent observance of a concomitant osteomyelitis [3, 58]. Septic arthritis due to other organisms is usually treated for 2–3 weeks.

Appropriate oral antibiotic choices for septic arthritis include cephalexin (100 mg/kg/day in three to four divided doses), clindamycin (30–40 mg/kg/day in three divided doses), and dicloxacillin (75–100 mg/kg/day in four divided doses) [3].

Prognosis

In modern medicine the case fatality rate of septic arthritis is less than 1%, but poor outcomes still occur [44, 75, 78, 151]. The weight-bearing joints of the hip, ankle, and knee are the most common to have sequelae [75]. Involvement of the hip joint has the worst prognosis with sequelae in up to 50% of patients in comparison to 12% with involvement of other joints [42]. The shoulder also has a propensity for poor outcomes and a complicated disease course due to delay in diagnosis and surgical intervention [126]. Complications of septic arthritis include articular destruction with ankylosis, growth disturbances, concomitant osteomyelitis or soft tissue extension, and hip dislocation [112, 126, 137]. The main predictors of a poor outcome include age less than 1 year, involvement of the hip and shoulder, concomitant metaphyseal osteomyelitis, duration of symptoms for 4 or more days before surgical intervention and initiation of antibiotic therapy, and a prolonged time in clearing the infection from the synovial fluid [40, 42, 45, 64, 77, 107, 117, 137, 150, 151]. *Enterobacteriaceae* is associated with increased frequency of sequelae in some literature reports [152, 153], and it is known that *S. aureus* is more virulent in comparison to *H. influenzae* [3, 14].

Summary

Septic arthritis must be in the differential in any child presenting with joint inflammation, refusal to move a joint, and/or constitutional symptoms as a prompt diagnosis and treatment decreases associated morbidity. Physicians need to expedite a laboratory and radiological evaluation, drainage, and prompt antibiotic initiation for best patient outcomes.

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Salmonella Arthritis

5

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Abbreviations

DMARDs	Disease-modifying antirheumatic drugs
EFS	Enteric fever syndrome
LPS	Lipopolysaccharide
NSAIDs	Non-steroidal anti-inflammatory drugs
RA	Rheumatoid arthritis
ReA	Reactive arthritis
SA	Septic arthritis
SCV	*Salmonella*-containing vacuole
SPI-1	*Salmonella* pathogenicity island 1

Introduction

Salmonella spp. can affect joints by causing either reactive arthritis (ReA) or septic arthritis (SA). ReA is part of spondyloarthropathies [1], which are a large family of diseases recognised by sharing the presence of HLA-B27 [2]. It has been historically defined as a sterile joint inflammation [3], which is a consequence of gastrointestinal tract infections caused by enteric bacteria, including *Salmonella* [4]. Its classical manifestation is synovitis of the affected joints [5]. On the contrary, SA is known for being predominantly monoarticular and painful and for the presence of bacteria on synovial fluid analysis [3]. This chapter discusses the relevant aspects of ReA and SA.

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Historical Aspects

During the nineteenth century, enteric fever syndrome (EFS), also known as typhoid fever, was an important cause of illness and mortality in the unsanitary and overcrowded urban conditions of Europe and the United States [6]. EFS is characterised by a severe systemic illness with fever, abdominal pain and diarrhoea. This underlying aetiology corresponds to the bacterium *Salmonella enterica* serotype *typhi* [6].

In 1880, German scientists Karl Joseph Eberth and Edwin Klebs competed to prove the aetiology of typhoid fever [7]. After performing 23 autopsies on patients who died because of typhoid fever, Eberth recovered '*Bacillus typhosus*' from the spleen in 12 of these patients and from Peyer's patches in 6 [8]. However, he did not identify this bacillus in the autopsies of patients without typhoid fever [7]. In 1881, Koch observed the bacillus in the kidney, spleen and liver of a dead patient. In 1884, Gaffky cultured the bacillus using newly developed techniques for bacterial solid culturing [7]. To satisfy Koch's criteria, Gaffky inoculated the grown bacillus in almost 60 animal species, without a positive result confirming salmonellosis as a human-specific disease. He also described its aetiology, mode of infection and prophylaxis [7]. The disease associated with *Salmonella* is typically a severe enteritis characterised by fever and gastrointestinal symptoms; however, the involvement of other tissues and organs, including joints, is possible [6]. Different cases of *Salmonella* arthritis have been reported in the literature since the last century [9]. Although ReA and SA are unusual, they are the main presentations of *Salmonella* joint involvement [10]. An important review published in 1990 reported different cohorts and reviews of patients with *Salmonella* arthritis [10]. David and Black reported a total of 84 cases of SA in 1960 following an exhaustive literature review in the pre-antibiotic era [11]. Another author reported a review of extra-intestinal cases of *Salmonella* in the antibiotic era until 1983, reporting a total of 44 cases of SA [12]. In 2013, a systematic review on ReA reported a total of 474 cases of *Salmonella*-associated ReA [13].

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_5

Epidemiology

In most cases, SA affects people in early or late stages of life [14]. It is predominantly monoarticular, and it occurs in large joints. The most affected areas are the knees, hips, shoulders, ankles and wrists [15, 16]. Its incidence varies depending on the population examined, with 4–10 per 100,000 inhabitants per year in the general population [14, 17]. Additionally, the mortality rate has been reported as 12% [15], with residual impairment of the affected joint in 61% of cases and complete recovery in 25% [15]. The majority of cases are reported in men [14, 15, 18]. The synovial fluid cultures of large cohorts of patients demonstrated that its presence is infrequent, comprising <1% of samples, compared with that of *Staphylococcus aureus*, which has been reportedly found in 62–100% of cases [15, 16, 19]. Some predictors of poor prognosis in bacterial arthritis have been described. Rheumatoid arthritis (RA) is the principal predictor, with an incidence of infectious involvement of 0.3–3% and a mortality rate of up to 20% over time in patients with RA where the involvement is monoarticular versus 71% when it is polyarticular. Other factors include the presence of a joint prosthesis, female gender and polyarticular involvement [15, 16].

Reports of studies conducted in the 1990s demonstrate that 2% of gastrointestinal infections caused by *Salmonella* were followed by joint involvement [16, 20]. Similarly, a retrospective study investigating the primary site of infection found that 13% of cases had a gastrointestinal origin, among other anatomical sources [15].

In developing countries, *Salmonella* is the cause of joint inflammation in one-third of the cases of ReA [21]. This gram-negative bacillus is likely to be present in adults aged >60 years, whereas it is rarely reported in children [22]. Of patients that develop ReA, 20% later develop ankylosing spondylitis [23].

Basic Microbiology of *Salmonella*

Salmonellae are gram-negative, non-spore-forming, flagellated, facultatively anaerobic bacilli. Three antigens are important for its virulence and classification: antigen H or flagellar antigen, antigen O or somatic antigen and antigen Vi [24]. The cell envelope of *Salmonella* comprises a complex net of lipopolysaccharide (LPS), which can function as an endotoxin, being an important determinant of *Salmonella* virulence [24]. The two main species are *S. enterica* and *S. bongori*. *S. enterica* is subdivided into six subspecies, including ~2600 serotypes [25, 26]. *Salmonella* cells have a diameter of 0.7–1.5 μm and a length of 2–5 μm [27]. These bacilli are characterised for being chemotrophs; they obtain energy from organic sources by oxidation and reduction reactions [27]. *Salmonella* spp. are intracellular pathogens, and certain serotypes, known as typhoidal serotypes, are pathogenic [28]. The serotypes or serovars are classified according to the O and H antigens using the Kauffman–White classification [29].

Salmonella species have some important virulence factors. *Salmonella* pathogenicity island 1 (SPI-1) is present in almost all serovars of both *S. enterica* and *S. bongori*, and it plays a key role in the intestinal phase of *Salmonella* infections [30–32]. This genomic island is one of the oldest in *Salmonella* spp., and it is hypothesised that the acquisition of this pathogenicity island conferred *Salmonella* an enteric pathogen [33]. SPI-1 has a length of ~40 kb [34], and its expression is induced by certain environmental signals that are usually present in the intestinal environment. These genes are also repressed when *Salmonella* colonises an intracellular compartment [31, 35, 36].

Pathogenesis

The first step in the pathogenesis of *Salmonella* accounts for the ingestion of the bacterial inoculum, usually via the faecal-oral route. Following the ingestion of the pathogen, the bacteria must survive the acidic environment in the stomach. *Salmonella* exhibit an increased tolerance for acid when exposed to moderately acidic environments (pH 4–5) [37]. Following survival and passage through the stomach, *Salmonella* bacilli must compete against normal flora to colonise [38, 39] and to survive and counteract host defence mechanisms, including bile salts, pancreatic enzymes, Paneth cell antimicrobial peptides and secretory IgA [40, 41].

Once the bacilli have colonised the intestine epithelium, adherence must occur, which is mediated by different genes that code for proteins, such as fimbriae [42, 43]. Invasion commences only after complete adherence and is regulated by genes in the invasion operon. Invasion mainly occurs in the epithelium that covers the Peyer's patches where M cells reside [44]. These cells are specialised in internalising the material from the lumen to the subepithelial space where antigen-presenting and T cells reside. *Salmonella* bacilli can also invade the subepithelium via enterocytes or dendritic cells present in the epithelium [45, 46].

When invasion is completed, the *Salmonella* bacilli that are internalised in phagosomes allow the expression of certain genes that modify these phagosomes, inducing the formation of the *Salmonella*-containing vacuole (SCV), where the bacilli express a type III secretion system to secrete all the virulent and structural proteins needed to survive, replicate and induce a potent inflammatory response. Once the bacilli are internalised, the risk for bacteraemia is high [47, 48].

Reactive Arthritis

After *Salmonella* has invaded via the gastrointestinal tract, a majority of patients develop enteric fever (typhoid serovars) or self-limited gastroenteritis (non-typhoidal serovars). However, some can develop complications and extra-intestinal manifestations. ReA is one of these conditions; it develops 1–4 weeks following *Salmonella* infections, and the bacterium is not located in the joint [49]. The pathogens most closely associated with ReA are *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter* and *Chlamydia trachomatis*, which is the most common cause of ReA with a genital origin. It is important to know that all of these pathogens are gram-negative bacteria, which have LPS present in their outer membranes [50, 51].

The immunopathogenesis of ReA remains to be fully elucidated; however, it has been found that certain antigens from pathogens are present in the joints despite the bacterial cultures of synovial fluid being negative [52, 53]. This suggests the persistence of the bacilli outside the joints, mainly in the gut subepithelium, allowing monocytes to transport pathogenic antigens to the joints [54, 55]. The persistence of the pathogen in the gut or lymph nodes has been associated with certain patients having dysregulated cytokine production and/or function, which allows the persistence of the bacteria in the organism [56, 57].

A defective $CD4^+$ Th1 response has been proposed as patients with ReA reportedly present with low levels of tumour necrosis factor (TNF)-α and interferon (IFN)-γ [58, 59]. Conversely, the Th2 cytokine profile appears to be more active in ReA [60]. Reportedly, the Th17 profile [interleukin (IL)-17] plays the most important role in the pathogenesis of ReA as patients with this condition present with high levels of IL-17 in the synovial fluid [61, 62]. In patients with *C. trachomatis*-induced ReA, an increased percentage of $CD4^+$ T cells and IL-17 has been detected in the synovial fluid [63, 64]. *Salmonella* ReA in mice is suggested to be dependent on a Th17 profile response [21, 65].

Septic Arthritis

In the case of SA, the pathogenesis is simpler. Joint invasion by pathogens occurs from haematogenous spread in a majority of patients. Trauma, surgery and infiltration can also be mechanisms of infection [66–68]. Once the bacteria have colonised the joints, they are able to rapidly proliferate and initiate an inflammatory acute response mediated mainly by IL-1ß and IL-6 [69, 70]. The innate response is mounted, and monocytes and neutrophils begin migrating to the synovial space, making inflammation worse [71] and activating an adaptive immune response of the Th1 profile [72], which in turn improves the bactericidal mechanisms of phagocytes, worsens inflammation and causes tissue destruction [73]. Figure 5.1 summarises the two pathological events.

Clinical Manifestations

Joint infection has a pattern of clinical presentation regardless of the causative pathogen. Pain is the main symptom that is present in up to 85% of the cases, followed by joint swelling and fever with a temperature of up to 38.5 °C [74]. However, it is important to state that some patients may not

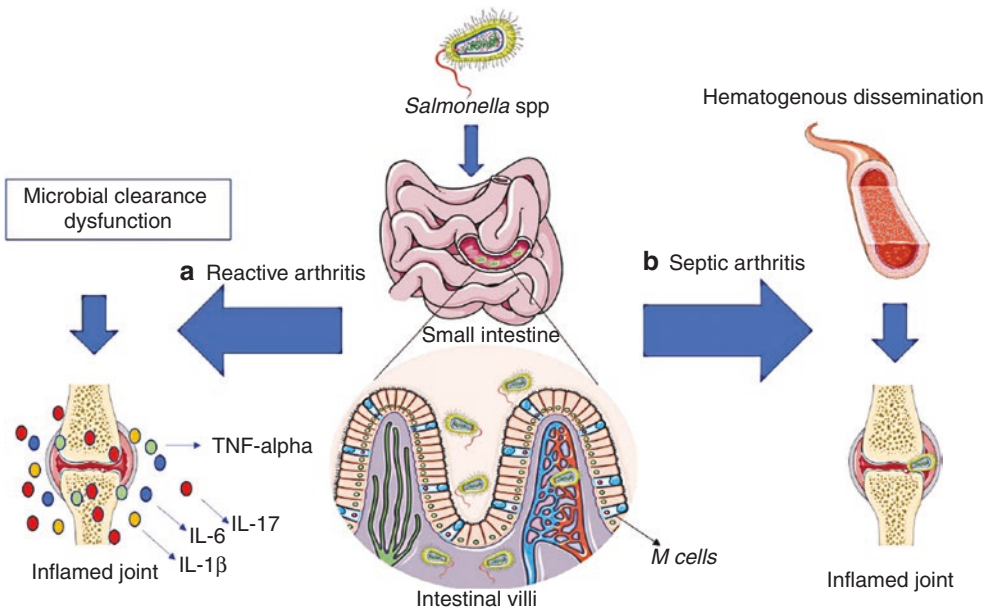

Fig. 5.1 *Salmonella* arthritis pathophysiology.(**a**) After *Salmonella* intestinal colonisation and infection, a person with a genetic and environmental susceptibility related with factors that affect microbial clearance will probably develop reactive arthritis. (**b**) After *Salmonella* intestinal colonisation and infection, haematogenous dissemination might occur, allowing for joint seeding of *Salmonella* bacilli and the development of septic arthritis. Images are taken from SMART (Servier Medical Art), a free copyright website for medical and scientific illustrations; they are available at https://smart.servier.com

present with hyperthermia [10, 75, 76]. Movement limitation is also observed [74], and serum tests may reveal elevated erythrocyte sedimentation rates, C-reactive protein and leucocytosis [74, 75, 77].

Despite the wide range of recognised *Salmonella* serovars, *S. enterica* subspecies are recognised as the main serovars responsible for the development of human diseases. Therefore, the clinical presentation depends on the serovar involved [78]. In the United States, the *enteritidis* serovar is the most important cause of food-borne infection, whereas the *typhimurium* serovar is the main cause of typhoid fever [21, 79].

Salmonella arthritis is often associated with gastrointestinal tract infections, either as a sequela or as a coexisting condition. The former is more common than the latter; therefore, it is termed ReA [21]. In a study involving 97 patients with *Salmonella* arthritis, 38 presented with diarrhoea, abdominal pain and vomiting symptoms that lasted for an average of 11 days [5], 8 with urogenital symptoms and 3 with eye symptoms [5, 20]. Uveitis is the principal ocular manifestation of extra-articular involvement reported in the literature; dactylitis and enthesitis have also been described [76].

A cohort of 11 patients demonstrated that the time between intestinal infection and ReA was ~15–30 days [76, 77]; however, studies involving animal models have confirmed that there is a negative effect on the joint from day 5 of the initial gastrointestinal manifestation [21].

One of the characteristics that leads to the suspicion of reactive infection caused by *Salmonella* is the involvement of two or more joints [17, 76], which occurs more frequently in patients with comorbidities, including systemic lupus erythematosus, spondyloarthropathies and RA [17, 80].

In certain patients, symptoms can disappear within several weeks, whereas symptoms in others can persist over years [21]. In the latter, it is distinguished as a disease based on the chronic presence of immune complexes indicative of a long-lasting *Salmonella* infection [81]. In cases wherein sickle cell anaemia is underlying, the infection may last for >2 months, is periarticular and is associated with osteomyelitis [82].

Diagnosis

Clinicians should always assess the complete clinical history to identify possible exposure to contaminated food or water [78]; previous infections and gastrointestinal and urogenital symptoms [76]; comorbidities involving connective tissue, autoimmune or autoinflammatory diseases or sickle cell anaemia [74, 80, 82]; joint surgery and replacement; trauma; and medications, including anti-TNF-α agents [77].

The clinical approach must take into account the above-mentioned features. Characterising the symptoms allows for an appropriate treatment approach; therefore, it is crucial to investigate whether there is monoarticular or polyarticular involvement and whether the symptoms are inflammatory or non-inflammatory [22]. Additionally, the presence of the classical signs of inflammation (swelling, tenderness, pain, movement limitation and redness) or synovitis increases the suspicion of a joint infection [10].

It is essential that the collection of aspirates from the involved joints, blood and stool cultures and Gram staining [17] are performed to confirm the isolation of *Salmonella* and permit a diagnostic confirmation [83]. It is important to state that gram-negative bacilli are positive in 50% of Gram stains, and joint cultures are positive in almost all cases of non-gonococcal bacterial arthritis [3]. Synovial fluid analysis provides detailed information to identify bacterial infection, including glucose consumption together with elevated lactate dehydrogenase; however, its specificity and sensibility to provide a diagnosis remain low [17]. In scenarios where the articular space is difficult to access, arthrocentesis may be guided by ultrasound [17].

There are key points enabling the differentiation between ReA and SA caused by *Salmonella*. In ReA, positive stool or blood cultures can be observed in addition to negative joint aspirates, whereas in SA, positive joint aspirates are observed. In terms of clinical presentation, ReA is defined as polyarticular and migratory, whereas SA is usually monoarticular [10].

Most of the serum inflammatory markers are unspecific. Conversely, procalcitonin has 93% sensitivity and specificity for SA compared with other acute phase reactants [84]. HLA-B27 supports the reactive form of infection due to *Salmonella*, and it is positive in 42–88% of patients. Studies suggest an important association between this marker and severe and long-lasting diseases rather than augmented susceptibility to the infection [5].

Imaging techniques, including simple radiography, computed tomography, magnetic resonance imaging and ultrasound, in the acute phases of the articular involvement are useful to identify evidence of effusion, osteomyelitis, arthritis and soft tissue oedema [3]. Gammagraphy also reportedly assists in the diagnosis of polyarticular involvement [85].

Treatment

Reactive Arthritis

ReA treatment focuses on providing symptomatic and supportive care. Antibiotics are not used usually; these are only indicated in ReA induced by genital pathogens when the infection is still active [86]. In the case of *Salmonella* infection, which is an enteric infection, evidence shows that the use of antibiotics does not improve the likelihood

of symptoms remission [87–91]. The mainstay of ReA treatment is the use of non-steroidal anti-inflammatory drugs (NSAIDs); however, the disease is usually self-limited, and the use of NSAIDs is directed to symptom relief only [49, 92].

When there is an inadequate response to NSAIDs treatment, intra-articular or systemic glucocorticoids can be used [49, 93, 94]. When the patient develops a chronic arthritis (≥6 weeks), non-biologic disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine or methotrexate, can be used [95]. If there is no sufficient response, the use of biological therapy with TNF inhibitors has been reported [76, 96].

Septic Arthritis

Antibiotic treatment is the mainstay of treatment for SA. In the case of gram-negative bacteria, including *Salmonella*, a third-generation cephalosporin is an ideal antimicrobial agent (ceftriaxone, ceftazidime or cefotaxime) [97, 98]. The antibiotic should be administered intravenously for at least 14 days, following which an oral course of fluoroquinolone must be administered of 14 days. Joint drainage is also recommended when there is a purulent collection [98, 99]. Providing symptomatic treatment is also encouraged [98].

Future

Research on working towards the identification of early diagnostic essays has already commenced. HLA-B∗27:05 reportedly binds to the peptides of the outer membrane proteins of *Salmonella* and functions as stimulators of T cells [4]. A lack of highly specific and sensitive biomarkers for *Salmonella* arthritis still exists; therefore, continued investigations are required to achieve diagnosis in the early stages of the disease, ideally with less invasive procedures and faster results. In addition, although it is an infrequent condition, it can lead to complications and mortality. Therefore, enhanced warnings and prevention are required by clinicians to reduce its incidence.

Acknowledgment The authors declare no conflicts of interest. There is no financial support.

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Brucellar Arthritis

6

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History

Isolation of the *Brucella* sp. pathogen occurred in 1887 when the British physician Sir David Bruce managed to isolate the *Micrococcus melitensis* organism from the spleen of febrile patients dying in the island of Malta. He also described what we now know as brucellosis as a "long-term disease, with fever and profuse sweating, splenomegaly, frequent relapses, nerve or rheumatoid pain, inflammation of the joints, and orchitis" [1]. However, many centuries earlier Hippocrates in his book *Epidemics* already described a picture like brucellosis that was suffered by people living on the Mediterranean coast [2]. Brucellosis is also commonly known as Malta fever, Mediterranean fever, Cyprus fever, undulating fever, and Tifomalárica fever [3]. Kulowski and Vinke in 1932 described the first case of *Brucella* spondylitis after isolating *Brucella melitensis* from a paraspinal abscess [4]. On the other hand, in 1958 Ganado and Craig found that 2% of 6300 patients with brucellosis had spinal injuries. In the year 1951, in Argentina, de Anquin found an incidence of *Brucella* spondylitis in about 50% of their patients related to the variety *melitensis* [5, 6].

Epidemiology

Human brucellosis is endemic and is often recognized as an occupational disease in developing countries as well as in rural regions of developed countries [7]. Its worldwide incidence is often difficult to determine [8]. It represents a public health problem, especially the *melitensis* variety, for some Mediterranean countries, south-central Asia, and some regions of Africa and Latin America [9]. There is no gender predominance; however, women can develop a more severe form of brucellosis [10–12], with greater joint involvement [13] and more severe thrombocytopenia [14]. The pediatric population is less affected (they represent 20–25% of cases) [15]. It has been reported that the *melitensis* variety can produce symptomatology in 50% of the members of a family [10, 16].

The estimated incidence in the Mediterranean rim and in the Middle East is 100 cases per 100,000 people-years [17]. According to WHO, there are around five to six million cases of brucellosis worldwide and 500,000 new cases are reported annually [7, 18–20]. In the United States, 4–10% of the cases are recognized, perhaps by the influx of unpasteurized dairy products [21]. On the other hand, the incidence of *Brucella* spondylitis may range between 2%and 53% [22].

The Pathogen

Brucellosis constitutes a zoonosis in which the causative agent is *Brucella* sp., an intracellular bacterium transmitted from animals to humans [8]. This bacterium is a non-mobile gram-negative coccobacillus, of slow growth, aerobic, and catalase positive, belonging to the group A2 of *Alphaproteobacteria*, together with *Bartonella henselae* and *Agrobacterium tumefaciens* [23, 24]. There are several species of *Brucella*, which are classified according to the host that hosts them [25–29]:

- *B. melitensis* (the cause of Malta fever): Reservoirs are goats, sheep, and camels.
- *B. abortus* (cause of Bang's disease): Cause of abortion in cattle.
- *B. suis:* Cause of abortion in pigs.
- *B. canis*: Isolated in abortions of beagle dogs.
- *B. ovis* and *B. neotomae*: Isolated in sheep and wood rats, non-pathogens for humans.

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_6

- *B. ceti*: Isolated from marine mammals such as whales, dolphins, and porpoises.
- *B. pinnipedialis*: Isolated in seals and walruses.
- *B. microti*: Isolated from red foxes in central Europe.

Of these, four are traditionally pathogenic for humans [7, 21, 30]: variety *melitensis*, *abortus*, *suis*, and *canis*.

Microorganisms can survive in unpasteurized goat cheese for more than 8 weeks and die within 60–90 days in cheese, resulting in lactic acid fermentation, and are eliminated in urine, feces, and animal-conception products and are viable for 40 days or more [8]. It is important to emphasize that the freezing of dairy products or meats does not guarantee the death of the bacteria unlike pasteurization and boiling [8]. Both the low number of virulent organisms and their adequate aerosolization capacity make it possible for this bacterium to be difficult to eradicate since its discovery, even in developed countries [2].

Transmission Mechanism

Humans happen to be accidental hosts. Infection is acquired through the gastrointestinal tract by means of the consumption of liver (viscera), raw meat, and milk products of goat, ovine, or bovine origin, especially if they are not pasteurized [15]. Transmission between humans is unlikely, but cases of transmission via the transplacental pathway [8], bone marrow transplantation [31], blood transfusion, and sexual intercourse are reported [11]. On the other hand, being considered an occupational disease among veterinarians, ranchers, and handlers of dairy products and meats, the most common transmission pathway is usually inhalation or conjunctival inoculation of the bacterium. Another route of common transmission between slaughterhouse workers is by contact of skin and mucous membranes eroded with bones and viscera of the animal [8].

Microbiology

The genome of *B. abortus* was decoded in 2001 and of the subtypes *melitensis* and *suis* in 2002 [32, 33]. For the detection of the bacterium, extended crops of up to 6 weeks are usually used using liquid or solid culture media or with the medium of Ruiz-Castañeda, since the crops are rarely positive before 10 days and could take up to several weeks. Automated cropping systems (such as the BACTEC) are more sensitive and usually positive within 7 days, but should be retained for 3 weeks. Bone marrow culture is seldom needed. The bacterium and its subtypes can also be detected using molecular diagnostic techniques such as the restriction fragment length polymorphism based on PCR (polymerase chain reaction) or the fluorescence in situ hybridization assay based on 16srRNA [8].

Pathogenesis

The bacterium, especially the subtype *melitensis*, is acquired by mouth. The incubation time is 2–3 weeks and includes invasion and multiplication within macrophages [15]. Its replication also usually takes place in dendritic cells, trophoblasts, microglia, fibroblasts, and epithelial and endothelial cells [2]. Immunity against *Brucella* infection is supported by the activation of antigen-specific T cells and in humoral responses. The pathogenicity of *Brucella* is very particular, since being an intracellular organism limits its exposure to the immune system; moreover, it does not present classical virulence factors and the lipopolysaccharides of its membrane are not typical. Currently, genes involved in structuring the virulence factors responsible for the processes of phagocytosis, fusion of phagolysosome, secretion of cytokines, and apoptosis have been characterized [34].

Upon invasion, *Brucella* adheres to the mucous membrane of epithelial cells through receptors containing sialic acid and sulfated residues [35], inducing activation of GTPases that are responsible for commanding the rearrangement of the cytoplasmic membrane to facilitate the entry of the bacterium, as well as activation of a mitogenic-dependent signaling pathway [36]. Once internalized, *Brucella* is detected by tissue lymphocytes and then transported by the lymphatic system to the regional lymph nodes and then via hematogenous spread to the rest of the organs, especially to the reticuloendothelial system. Localization in some organs can be associated with the presence of cellular infiltration with or without granulomatous formation, caseification, necrosis, or formation of abscesses. Shortly after its entry, both neutrophils and activated macrophages migrate to the initial point of entry. The innate immunity system is in charge of the initial response, which includes activation of Tγδ cells, natural killer (NK) cells, and CD4 and CD8 cells. The lipopolysaccharides (LPS) of the surface of the bacterium are recognized by these cells, which send signals to activate macrophages and facilitate phagocytosis of the bacterium. The bacterium enters macrophages by particular lipid-dependent structures of its own cytoplasmic membrane, known as uniform lipopolysaccharides (LPS-U), which are essential for its survival within infected macrophages. However, its immunogenicity is greatly inferior to the LPS of other gram-negative agents. It is believed that the unnoticed nature of *Brucella* is due in part to their LPS since these are weak agonists of the TLR4 so they would activate weakly the PI3K [37].

Tγδ cells promote the initial production of IFN-γ, TNF-α, and other cytokines, which become cytotoxic for monocytes

infected by *Brucella* and for the bacterium itself, hindering its intracellular survival. The Th lymphocytes secrete cytokines that activate mechanisms of intracellular death of macrophages infected with *Brucella*, known as "oxidative burst" or "oxygen-based death," which consist of the production of hydrolytic enzymes and activation of the peroxide-halide system. Only 10% phagocytized bacteria manage to survive, which will go to a period of adaptation within the phagocyte. These bacteria will be lodged inside a special vacuole, called "*Brucella* container vacuole" (BCV), which acts as a replicative compartment or brucellosome [38], where the mechanisms are activated to produce acidification and with the same promotion of survival of bacteria [8]. In parallel, *Brucella* will express a type IV secretion system (T4SS) which allows it to survive and multiply, being essential for its prolonged permanence [39].

During the infection, the surviving *Brucella* progressively recover all their functions, especially the reactivation of the transcription-translation, including those related to the genes of virulence [40–42]. Within the adaptation strategies, *Brucella* creates transcription mechanisms that favor the inhibition of apoptosis of infected monocytes, prevent the maturation of dendritic cells, reduce antigen presentation, and reduce the activation of virgin T cells [43]. In addition, *Brucella* can withstand death by oxidative burst using the hydrogen peroxide-halide system-myeloperoxidase [8].

Several studies indicate that an immune defect occurs during the invasive phase of infection. Although TH1 cells are responsible for commanding the response to *Brucella*, especially the CD4 and CD8 T cells [44], disease will occur due to a deteriorated response of Th1, defective T-cell proliferation, defective production of IFNγ, and poor quality of the cytotoxic activity of NK. However, studies in murine agents showed that the role of these cells was almost negligible [45].

On the other hand, IL2 produced by B cells and macrophages favors the response by TH1 and the induction of IFN-γ, whose activity is maximized by TNF-α produced by macrophages and NK. Induction of colony-stimulating factor dependent on IL1 increases the infiltration of macrophages and neutrophils into the spleen. The splenocytes come to express high levels of mRNA for IL2, IFNγ, and IL10 and low levels of mRNA for IL4 [46]. T4SS is the factor that produces a state of long-lasting infection to *Brucella*, making it clear that resistance mechanisms are not sufficient for the success of infection [44]. Studies in murine systems showed evidence that TLR2 or TLR4 deficiency generates a poor ability to control infection, unlike those MyD88-deficient cells which suffer a dramatic increase during brucellar infection [47].

Brucella can withstand the death mediated by lysosome and acidification by phagosome, continuing its multiplication in the endoplasmic reticulum of macrophages without affecting the integrity of the host cell. It evades the intracellular destruction by restricting the fusion of BCV to the lysosome, since it modifies the structure of this vacuole as well as of the endoplasmic reticulum, so that the BCV acquires autophagic function and positivity for the protein 1 associated to lysosomal membrane [48]. Subsequently, organisms are released by induced cell necrosis and lysis.

The virulence mechanisms of the bacterium will determine the survival or death of the infected macrophages. It is believed that one of the factors that impede the cellular uptake of the organism is the absence of the sensory-regulatory system BvrR/BvrS, because it originates important changes in the external bacterial membrane [46]. *Brucella* protects the infected cells from apoptosis in a mechanism that uses IFN-γ or TNF-α. In the initial stage of infection, *Brucella* increases the activation of the pathway AMPc/PKA which regulates a variety of mechanisms that favor *Brucella* infection by preventing the removal of host cells and favoring that macrophages become apoptosis-resistant [8].

Antibody-specific production as a response from the host to *Brucella* occurs immediately after infection. During the first week, IgM versus LPS appears in the serum. A week later, IgG and IgA appear and their peaks are reached during the fourth week. The appearance of anti-LPS antibodies has a limited role in defense against infection; however, they are important in diagnosing the disease.

Diagnostic Methods

Both serological and bacteriological methods may be used for the detection of *Brucella*; within the serological methods [49] currently available are Rose Bengal and 2-mercaptoethanol, molecular tests include PCR and ELISA, and bacteriological cultivation is also performed. In most cases diagnosis will be carried out by serology [50, 51]. However, the isolation of the bacterium in a culture medium (blood, tissue, or bone marrow) is the one that will provide definitive diagnosis.

Serological Methods

- *Rose Bengal*: Used as a screening for brucellosis. It is a rapid test that specifically detects IgG1-type antibodies against *Brucella* sp. It allows discrimination from cross-reactions or false positives. It has high sensitivity in acute brucellosis, close to 99%, although low specificity [52]. It is not useful in the follow-up of patients because it remains positive despite good evolution of the treatment.
- *Plate agglutinations*: Introduced by Wright, this test detects both IgG and IgM antibodies [53] which will attack the smooth lipopolysaccharides (LPS), so it can

give *cross-reactions with other bacteria* (*Salmonella group N*, *Vibrio cholerae*, *Escherichia coli O157*, *Yersinia enterocolítica*, *Francisella tularensis*, and *Stenotrophomonas maltophilia*, among others) [54]. It reacts quickly at the onset of an infection and may remain positive up to 2 years after successful treatment [55].

- *Tube agglutinations*: This test provides quantitative information by giving the result in titers in relation to the immune response against *Brucella* antigens. It is the most widely used technique in endemic countries [56]. Serial agglutination of serum in tube is carried out. It detects IgG2 and IgM antibodies. A titer ≥1:80 is considered positive in non-endemic regions and titer≥1:320 or even ≥1:160 in endemic regions. The main limitations that this test presents are that it takes a long time to do it, people in contact with livestock in endemic areas can show high degree of antibodies against *Brucella*, there is possibility of cross-reaction with other bacteria, and this test cannot identify acute cases from chronic [57–59].
- *2-Mercaptoethanol*: Used to detect IgG antibodies. It is based on the degradation of IgM due to the action of the radical thiol containing 2-mercaptoethanol. It is very useful in chronic infection in which the tube agglutination test may exhibit a low titer, since the serum will contain only IgG antibodies. In addition, decreased titers of IgG would indicate efficacy of treatment.
- *Coombs test*: It is not routinely performed due to its complexity, takes a long time to perform, is laborious, and needs a trained staff [56]. Nevertheless, it is useful in situations of a prozone phenomenon where false negatives can be obtained [60, 61] and where the evidence of agglutinations is negative despite having an evident clinical picture [62]. It is also the most sensitive method to confirm relapses [53].
- *ELISA*: This is a rapid test with a sensitivity and specificity greater than 80%. This test allows to measure the humoral immune response through the detection of IgM, IgG, and IgA antibodies [63–65] facilitating a better understanding of the condition of the disease. An advantage of its use is that it allows screenings of several patients to be performed simultaneously [66]. On the other hand, it has been reported to present high sensitivity to detect neurobrucellosis [53].

Regarding this technique, Mantur et al., to know its diagnostic certainty, published a study with 92 patients with clinical suspicion of brucellosis. All patients underwent tube agglutination for *Brucella*, 2-mercaptoethanol, culture, and ELISA [56]. It was found that the crop was positive in 33.6% and the agglutinations were positive in 25%, while the ELISA detected the disease in 60.9% of cases, reaching a sensitivity of 100% although a specificity of 71.3%. This study was used to show that ELISA is more sensitive than the agglutinations when detecting the disease in its acute and chronic phases. These results were like those previously found by Gad and Kambal and by Ariza et al. in their respective studies [67, 68].

Another interesting aspect of this study is that the ELISA could identify elevated values of IgM and IgG antibodies at any time of the disease. Other reports showed similar results to those of Mantur [67, 69, 70]. There is another simplified method of the ELISA called lateral flow assay (LFA), which can be used in both acute and chronic phases, is easy to interpret, and has a sensitivity and specificity greater than 90% [71].

Molecular Detection

Serological tests are sufficient for diagnosis; however, due to the possibility of cross-reaction or subsensitive reaction in samples from regions with low prevalence of *Brucella* infection, these tests might be proven to be unspecific [72]. Polymerase chain reaction or PCR has become quite relevant in the diagnosis of *Brucella*. This test is based on the detection of bacterial genetic material in biological samples (blood, cerebrospinal fluid, urine, post-mortem tissues) of both human and animal specimens and consists in conducting a specific amplification of bacterial DNA, when combining specific markers with DNA polymerase [73]. It is a fast and precise technique that contributes to an early diagnosis, especially during the acute phase of brucellosis, in addition to being useful during post-treatment follow-up and early relapse detection [74, 75]. It allows detection of more than 10 species of *Brucella* sp., and in low-income regions it will be used as an additional test in special cases of difficult diagnosis.

Currently there are several PCR techniques, such as real-time PCR, multiple PCR, and nested and semi-nested PCR, among others that are in development. However, all these tests do not yet have a standardized procedure that allows them to be used in a massive and equitable way between the various laboratories [76].

- *Conventional PCR*: It turns out to be more sensitive than microbiological methods both for the diagnosis of early detection and for relapses [77–79]; however, studies carried out by Baddour MM et al. and Navarro et al. showed that the efficiency of this technique depends on the specificity of the primers used [80, 81]. On the other hand, it has been seen that high concentrations of DNA from leukocytes and heme compounds can affect the results of PCR [82].
- *PCR in real time*: The advantage with respect to the conventional technique is that it turns out to be more economical and also allows the quantification of the nucleic

acids (number of copies of DNA, levels of expression of mRNA, and in other contexts, the viral load) [83–88]. It is a highly reproducible technique and of low cost and high speed and very sensitive and specific (90–100%). It is useful in initial diagnosis and to differentiate states of activity, inactivity, and seropositivity [76].

- *Multiple PCR*: It turns out to be useful because, in addition to minimizing expenses, it can recognize many pathogens at the same time [87]. It has high sensitivity and specificity, proving to be an alternative to crops. It also allows detection of *Mycobacterium tuberculosis* and *Brucella* sp. complex simultaneously. So it turns out to be a practical tool for the differential diagnosis of extrapulmonary tuberculosis and complicated brucellosis [88–90].

Bacteriological Method

The crop turns out to be the gold standard for the diagnosis of *Brucella*. The isolation of the bacteria in blood culture is possible in 40–70% of the cases (*B. melitensis* or *suis*), but with lower yield in the cases of *B. abortus*. The conventional method is the biphasic system of Ruiz-Castañeda [91], which is characterized by having a long incubation time of 6 weeks and sensitivity of 90% in the acute phase and 20% in the chronic phase [92, 93]. It can be optimized by using the method modified by Gotuzzo et al. who added sodium polyethylene sulfonate and cysteine. There is another culture method known as lysis centrifugation method [94] which differs from the previous one for the short time it takes to obtain the result [95]. Its sensitivity during the acute phase is also 90% and less than 70% in the chronic phase [94, 96]. Several publications indicate that the best method is culture of bone marrow versus repeated blood culture in two opportunities [97, 98] with a yield of 92% and with rapid growth. Culture of bone marrow is useful in situations that have high clinical suspicion against negative results of serological studies (recurrent uveitis, unexplained fever, hematologic abnormalities) [97, 99–101].

Clinical Spectrum

Brucellosis is an entity characterized by nocturnal fever, arthralgias, sweating, and splenomegaly. The most frequently affected organ systems are [102]:

- Osteoarticular in 20–30% of cases. It can be manifested by the presence of sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis, or bursitis [9, 103].
- Genitourinary by orchiepididymitis with 40% of cases.
- Hepatic abscess at 1%.
- CNS involvement at 1–2%.
- Cardiovascular or endocarditis with less than 1%.

Clinical Presentation

Brucellosis can be acute, subacute or undulating, and chronic [15].

- *Acute*: Nocturnal fever greater than 38 °C, sweating, general malaise, weight loss, and arthralgias. One-third of patients develop arthritis, myalgia and back pain, anemia, leukopenia, and hepatic involvement in 40–50%.
- *Subacute or undulating*: It happens after 2 months. It is the most common form of presentation in endemic areas, becoming the cause of fever of unknown origin [104], persisting up to 1 year. Hepatic and articular compromise is common.
- *Chronic*: Lasts longer than 1 year. Two types of patterns are described:
  - In the first there is back pain, arthralgias, sweating, and depressive mood, like chronic fatigue syndrome.
  - The second pattern is characterized by involvement of a more localized area as it occurs in spondylitis or uveitis, in the absence of fever or systemic symptomatology [104].

Osteoarticular Manifestations

Constitutional and musculoskeletal or osteoarticular involvements are the most common clinical manifestations seen in human brucellosis. Majority of infected individuals, more than 70%, exhibit both fever and general malaise during the acute phase, while 10–60% exhibit arthralgias, back pain, peripheral arthritis, sacroiliitis, spondylitis, osteomyelitis, and bursitis (Table 6.1) [9, 15, 103, 105, 106]. However, it is necessary to emphasize that clinical presentation of these forms of articular involvement depends on the phase of the disease, since arthralgias and peripheral arthritis will be seen in more acute cases, while sacroiliitis will be seen in subacute cases and spondylitis in chronic phase [15].

Table 6.1 Osteoarticular manifestations

	Frequency	Brucellosis: clinical form
Peripheral arthritis Knee Hip Shoulders Sternum-clavicular joints	25–50%	Acute
Sacroiliitis	15–33%	Subacute
Spondylitis	5–12%	Chronic
Extraarticular manifestations Tendinitis Epicondylitis Bursitis Fibrositis	10–15%	–
Osteomyelitis	<1%	Subacute/chronic

On the other hand, the presence of tenosynovitis is usually not frequent, although it has rarely been described [9, 107].

Peripheral Arthritis

It is a common articular manifestation and may present as monoarticular or asymmetric oligoarticular presentation [106], becoming part of the differential diagnosis of seronegative spondyloarthritis. Joints commonly affected include the knee, hip, and shoulders; however there may also be involvement of sternum and sternum-clavicular joints [108]. It is usually seen in children and young adults [15]. Peripheral arthritis may be septic or reactive in origin. *Brucella* septic arthritis usually has a monoarticular presentation, with presence of the bacterium in the joint as a result of hematogenous spread, although it may also be due to an adjacent infection as would happen in osteomyelitis [8]. The bacterium may be isolated from the joint fluid provided that a suitable culture medium is used (although it does not occur in all cases) [15]; however, synovial biopsies are not useful for differentiating septic arthritis from reactive arthritis because they share the same histological characteristics [15]. Its prognosis is favorable if the appropriate antibiotic is chosen, requiring surgical cleaning of the joint only in cases of poor clinical evolution. On the other hand, in *Brucella*-induced reactive, clinical presentation is usually oligo- or polyarticular and the bacterium is not isolated from the joint [109]. Clinical improvement occurs with systemic anti-inflammatory therapy, although it can also spontaneously remit [110–113]. Polyarticular involvement, symmetric or asymmetric, with occasional presence of rheumatoid factor positivity, which might be transient, may also occur [106, 114]. Of interest, leukocyte values in peripheral blood are normal in both septic arthritis and spondylitis [8]. The study of synovial fluid reveals a count of leukocytes between 400 and 4000 cells/mm^3 with 60% polymorphonuclear, glucose may be reduced, and the culture could be positive in up to 50% of cases [8].

Sacroiliitis

Sacroiliac joint involvement is usually seen in children and young adults, being unilateral and with a more subacute presentation [15, 115, 116]. Gotuzzo et al. in their prospective study found that in their series of 163 cases with brucellosis, sacroiliitis was the second most common that affected joints, 33.1% [117]. However, this frequency can range from 9% to 57%, and unilateral involvement is seen in over 70% [118–120]. Laségue sign can frequently be found in patients with sacroiliac joint involvement [117]. Asymptomatic sacroiliitis with negative and/or normal Schober's test may be seen in 20–40% of patients [20]. HLA-B27 positivity may be present in 45% of patients and MRI is a more sensitive technique than plain x-ray in the diagnosis of sacroiliitis. Clinicians should have a high index of suspicion for the presence of asymptomatic sacroiliitis.

Spondylitis

Spondylitis has a global frequency between 2% and 53% [121], and it is seen in 5–10% of patients with brucellar arthritis [106, 117, 122]. It is clinically characterized by the triad: lumbar pain, nocturnal fever, and sweating [103]. Although it may occur in the subacute phase of the disease, it is mostly going to be present in the chronic phase, affecting people over 40 years [15]. It usually affects one or more lumbar vertebrae, having a greater predilection for L4 [8], following in frequency the thoracic vertebrae and lastly cervical. Patients often complain of lumbar pain exacerbated in decubitus position, a characteristic that makes it possible to differentiate it from non-inflammatory pathologies. Clinically, *Brucella* spondylitis is manifested by pain to deep percussion of the affected vertebrae with limitation of axial mobility; in cases of compression, the patient will refer dysesthesia in extremities, decreased muscle strength, and alteration of the osteotendon reflexes [103]. Infection begins with erosion at the edge of the antero-superior region of the vertebral body, which is the most vascularized area of the vertebra, then taking the appearance of a blunt or rounded edge [8, 106, 123–125]. The infection will compromise both the vertebral bodies and the intervertebral disk, and paravertebral abscesses rarely occur [8]. Diskitis or narrowing of the disk space constitutes the earliest sign of involvement, although the concomitant presence of blastic and lytic lesions and the rapid repair of lesions evidenced by the presence of sclerosis and osteophytes in "parrot beak," also characteristic presentations of *Brucella*, allow differentiation from spondylitis by tuberculosis or Pott's disease [126–129].

The Role of Imaging Techniques

The important role of imaging studies in the diagnosis of *Brucella* spondylitis has been clearly defined in the past several years. Imaging studies have been shown to be of great utility in the differential diagnosis of pyogenic or tubercular spondylitis, which constitutes their main differential diagnoses. Of all available techniques, it has been clearly demonstrated that magnetic resonance imaging (MRI) is the preferred imaging modality [130]. Imaging techniques, especially MRI, facilitate early diagnosis, especially in incipient phases when clinical suspicion is high.

Evidence of spinal involvement by imaging studies will depend on the phase or stage in which disease is diagnosed.

During acute phases involvement of multiple vertebrae and a variety of bony lesions can be seen [131, 132]. In early stages, osteolytic destruction is evidenced by the presence of lamellar bone dissolution of terminal plates and vertebral body and with low degree of bone destruction mediated by osteophytes [131, 132].

In chronic brucellar spondylitis, the center of vertebral bodies is involved by the inflammatory process and hardened, preventing the bone from being destroyed. This is evidenced by the presence of hyperplasia, sclerosis, and formation of osteophytes type "parrot beaks," eventually forming bony bridges [133]. Sclerosis will be expressed by the presence of hyperplasia of the vertebral body, proliferation of osteophytes, formation of bone bridges, sclerosis of the vertebral plaque, and osteogenesis of vertebrae [134].

Conventional Radiology: Spine X-Ray

Conventional x-ray fails to demonstrate structural spine changes in early stages of disease in the majority of patients [103]. However, bone destruction and proliferation were common in chronic stages, with vertebral bone hyperplasia, destruction, and sclerosis around the lesion [103]. Overall, lumbosacral spinal involvement is more common and seen in over 70% of patients, while cervical involvement is observed in less than 10%. Lateral osteophytes and disk space narrowing are also frequently seen, more than 70%, in chronic stages [103, 133].

Computed Axial Tomography (CAT)

As with conventional radiography, tomography does not add much in early stages of brucellar spondylitis, but it is highly informative in chronic stages. Both bone destruction and and sclerosis are observed in over 80% of patients [103]. Lamellar osteolytic destruction of the terminal plate and vertebral body, marginal osteophytes, and bony bridges are clearly identified by CAT in the majority of patients [133].

Magnetic Resonance Imaging (MRI)

MRI demonstrates vertebral involvement in over 90% of patients and intervertebral involvement in 80%. Areas of bone destruction will be shown to be hypodense in T1 sequences and hyperdense in T2 and STIR sequences (fat suppression), while peripheral sclerosis is associated with hypodensity in T1 and T2 and soft tissues issuing hypointensity in T1 and hyperintensity or isointensity in T2 [133]. Paravertebral abscesses can be present in about 8% of patients [117]. More recent studies have clearly confirmed the utility of MRI for the early diagnosis of brucellar spondylitis due to its high sensitivity in recognizing bone infection [103, 135, 136].

Extraarticular Involvement (Table 6.2)

- *Hematological*: Anemia, leukopenia with lymphocytosis, or thrombocytopenia may occur; the latter is so severe that in some cases, besides the administration of glucocorticoids, it may require splenectomy. Pancytopenia secondary to granulomas in the bone marrow may occur [137] and depending on the area may have an incidence between 2% and 14% in adult patients [138]. Although it is rare, mesenteric lymphadenitis as part of the acute phase of brucellosis may also occur [139].
- *Genitourinary*: Cases of orchiepididymitis are reported in endemic areas and can present an evolution so torpid that it may require orchiectomy [140]. It can be seen in adults and children and can be uni- or bilateral. Women may develop dysmenorrhea, tubo-ovarian abscesses, salpingitis, or cervicitis [8].
- *Neurological*: It is usually rare, but severe. It may be expressed by meningitis, encephalitis, or meningoencephalitis; it is reported in up to 5% of adults; in children it is a rare complication [125, 141–144]. Unlike tuberculosis, *Brucella* does not involve cranial pairs. The characteristics of CSF are like those of a bacterial meningoencephalitis; however *Brucella* is cultivable and can also be found in elevated agglutinations in CSF but is occasionally not usually detected [8].
- *Gastrointestinal*: Although it is rare, clinical hepatitis cases have been reported in 3–6% of adults, and it can be severe in concomitant cases of bone and hematologic involvement [29, 145–148].

Table 6.2 Constitutional and extraarticular manifestations

	Frequency
Fever	70–95%
Malaise	70%
Hematological (anemia, leukopenia, thrombocytopenia, or pancytopenia)	2–14%
Genitourinary (orchiepididymitis, tubo-ovarian abscesses, salpingitis, or cervicitis)	40%
Gastrointestinal (hepatitis)	3–6%
Neurological (meningitis, encephalitis, or meningoencephalitis)	<5%
Dermatological (erythema nodosum, purpura, and petechiae)	<5%
Cardiovascular (endocarditis, myocarditis, pericarditis, aortic abscesses)	<2%

- *Cardiovascular*: It is rare, but endocarditis, myocarditis, pericarditis, aortic abscesses, mycotic aneurysms, thrombophlebitis, and pulmonary embolism [8] may occur.
- *Dermatological*: Erythema nodosum, purpura, and petechiae may occur (although more as a result of thrombocytopenia), as well as chronic ulcers, cutaneous and subcutaneous abscesses, vasculitis, and superficial thrombophlebitis [8].

Brucellar Arthritis in Children

Brucella infection is uncommon in children, occupying this population group by 20–25% in all reported cases of human brucellosis [15]. Even studies carried out during between the 1950s and 1970s revealed that infection in pediatric patients was more frequent in school age, beginning to decrease its frequency in children under 7 years old [123, 124]. Children usually have acute and subacute forms of infection, developing a mild to moderate disease. Within the articular manifestations, which are also the most frequent during the development of the infection, peripheral arthritis tends to predominate [15]. In their series of cases of 84 children published in 1988, Gotuzzo et al. found that as in adults fever was the cardinal symptom in 93.8%, followed by anorexia in 73.5% and general malaise in 68.2%, while hepatomegaly was the main clinical finding with 77%, followed by adenomegaly at 61.1%; the presence of arthritis occupied a fifth place with 44% [117]. In addition, in the same study, it was found that the joint involvement was more frequent as the children reached older age and that this had preference for peripheral joint involvement in 69% followed by 23% by sacroiliac involvement; in addition the study drew attention to the lack of axial involvement.

More recent studies in pediatric populations have confirmed Gotuzzo et al.'s findings [139, 149–152].

Differential Diagnosis

Because fever is the predominant symptomatology, clinicians are obliged to rule out brucellosis in patients with fever of unknown origin or persistent fever despite antibiotic administration, within an appropriate clinical-epidemiological background. Diseases that may resemble brucellosis include typhoid fever, tuberculosis, infectious endocarditis, and acute rheumatic fever [153]. This diagnostic investigation should be carried out especially if fever occurs in the context of an immigrant patient who in addition to fever presents with arthralgias or peripheral arthritis, as evidenced in a series of cases recently published [154].

Treatment

Before opting for any therapy, it should be clear that the most appropriate treatment for brucellosis should reduce morbidity, prevent complications, and above all reduce the rate of relapse [155]. Another important aspect to consider is the surveillance of adverse events that may occur during treatment, to ensure proper adherence to it. The treatment, although basically its duration, depends on the phase in which the infection is detected as well as the type of organ that is compromised.

A characteristic feature of brucellosis is its capacity to relapse after completion of treatment, which usually occurs after 3 to 6 months or even after 2 years [156]. Relapse is due to its intracellular property that allows the organism to be protected from the mechanisms of defense of the host [156]. Therefore, it is necessary to opt for a drug with an adequate in vitro action, as well as intracellular action, being tetracyclines as the drug of choice and the cornerstone of therapy added to the synergistic action of rifampicin, even though in vitro studies have demonstrated resistance of *Brucella* to rifampicin when used as monotherapy [117, 157–162]. Other drugs that have shown great effect in lowering the rate of relapse by being associated with doxycycline are aminoglycosides, especially gentamicin [163], although there is greater evidence with streptomycin.

At the end of the 1980s, WHO proposed a standard treatment based on two dual therapies: doxycycline 200 mg/day for 6 weeks combined with rifampicin 600–900 mg/day for 6 weeks or with streptomycin 1 g/day for 2 to 3 weeks, either to be used as first-line treatment [164, 165]. Subsequent meta-analyses confirmed the superiority of the combination of doxycycline-streptomycin over doxycycline-rifampicin in terms of relapses and therapeutic failures [166–170]. The reason behind the low efficacy of treatment with doxycycline-rifampicin is that the concomitant administration of rifampicin causes decreased serum levels of doxycycline [171, 172]. One aspect that also began to be considered, in addition to clinical efficacy, is the possibility of provoking resistance in *Mycobacterium tuberculosis* with the prolonged use of rifampicin in endemic areas [173]. Despite this evidence, the reason why in some situations it is preferable to use doxycycline-rifampicin is due to the low cost of the medication as well as the ease of administration by mouth [174, 175] and the possibility that the aminoglycosides can provoke nephrotoxicity and ototoxicity when used for long periods. Treatment recommendations were made by WHO and the International Human Brucellosis Meeting (Table 6.3) [165, 176].

Quinolones are other drugs that according to the literature can also be used as part of the combined therapy either with doxycycline or rifampicin. Although it turns out to be an alternative, this combination has controversial results

Table 6.3 Treatment recommendations made by WHO and International Human Brucellosis Meeting

Treatment	Frequency	Route of administration	Duration
Doxycycline 100 mg Streptomycin 15 mg/kg	Twice daily Once daily	Orally Intramuscular	6 weeks 2–3 weeks
Doxycycline 100 mg Rifampicin 600–900 mg (one morning dose)	Twice daily Once daily	Orally	6 weeks
Doxycycline 100 mg Gentamicin 5 mg/kg	Once daily	Orally Endovenous or intramuscular	6 weeks 7 days
Above treaments + TMP-SMX 800/160 mg	Twice daily	Orally	6 weeks

Adapted from Ariza et al. [165]

Table 6.4 Treatment of brucellar arthritis in children

Treatment	Frequency	Route of administration	Duration
TMP/SMZ 8/40 mg/kg/d Streptomycin 30 mg/kg/d or Gentamicin 5 mg/kg/d	Twice Once	Orally Endovenous or intramuscular	6 weeks 3 weeks 7–10 days
TMP/SMZ 8/40 mg/kg/d Rifampicin 15 mg/kg/d	Twice Once	Orally	6 weeks
Rifampicin 15 mg/kg/d Streptomycin 30 mg/kg/d or Gentamicin 5 mg/kg/d	Once	Orally Endovenous or intramuscular	6 weeks 3 weeks 7–10 days

since several studies have found that there is not much difference between those groups that used quinolones (including ofloxacin and ciprofloxacin) and those who did not use quinolones [177–181]. A meta-analysis of randomized clinical studies published in 2008 concluded that the combination of a quinolone with rifampicin was less effective than treatment with doxycycline-rifampicin or doxycycline-streptomycin [182]. On the other hand, a study published in 2012, which compared the use of doxycycline-streptomycin versus doxycycline-rifampicin versus rifampicin-ofloxacin, found that the group that received doxycycline-streptomycin presented greater clinic response, lower relapse rate, and therapeutic failure rate [178, 183, 184]. However, a recent study published in 2016, which compared patients receiving dual therapy with doxycycline-rifampicin versus triple therapy with doxycycline-rifampicin-levofloxacin for 6 weeks, found that the relapse rate was higher in the first group (22.6% versus 9.3%), a result that was similar to those previously found by Akova et al., Karabay et al., and Solera et al. [170, 177, 178], showing that there is an increase in resistance to dual therapy in the last several years [185].

Dual therapy with doxycycline-streptomycin is the choice for osteoarticular involvement [170, 186], and Gotuzzo et al. suggested that any of the two first-line regimens for a period of 4 weeks, with streptomycin being administered IM for 2 weeks, should be appropriate [117]. In cases of spondylitis and osteomyelitis, the recommendation is to prolong therapy that could last several months, with doxycycline to be used for 8 or more weeks. Need for surgery occurs rarely [176]. *Brucella* sacroiliitis does not require specific treatment.

In the case of chronic brucellosis, since it is difficult to diagnose, Gotuzzo et al. have suggested the use of immunomodulators. Although there are different treatment alternatives, cases of recurrence continue to persist over the years; that is why studies with the use of immunomodulators are under development. This is the case of hydroxychloroquine, widely used in the management of joint involvement of connective tissue diseases and which apparently has a positive impact on brucellar infection by favoring the creation of an alkaline environment that counteracts the intracellular acidification produced by *Brucella*, managing to destroy the phagolysosome [187]. In a recent study that compared the use of doxycycline-streptomycin versus doxycycline-streptomycin-hydroxychloroquine, favorable results in terms of clinical response and relapses were found in the second group compared to the first [188]. More studies are still in development.

In the case of pediatric patients under 8 years of age, WHO recommends avoiding the use of all tetracyclines, including doxycycline. Although to date there is no therapy of choice, what is recommended to use in this type of population are the aminoglycosides, cotrimoxazole, or rifampicin in combination therapies. As in adults, monotherapy is avoided due to the frequency of relapses. Treatment is successful with the use of TMP-SMZ (8/40 mg/kg/day) for 6 weeks together with streptomycin 30 mg/kg/day intramuscular daily for 3 weeks or gentamicin 5 mg/kg/day intravenous or intramuscular for 7–10 days. Other alternative treatments are those shown in Table 6.4[176].

Conflicts of Interest *EMM*: None. *KVV*: None.

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Prosthetic Septic Arthritis: Etiology, Clinical Aspects, and Management

7

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Etiology

Periprosthetic joint infection (PJI) is a relatively rare but potentially devastating consequence of total hip arthroplasty (THA) and total knee arthroplasty (TKA). Primary total joint arthroplasty (TJA) has become a common procedure with approximately 209,000 THAs and 450,000 TKAs performed in the United States (US) in 2005. As the US population continues to age, the need for these surgical procedures is expected to dramatically increase, with one projection predicting an increase in THAs and TKAs of 174% and 673%, respectively [1]. The historical incidence of PJI has ranged from 0.5% to 1% for THA and is approximately 2% for TKA [2, 3] although a recent retrospective study of patients who underwent primary THA or TKA in California hospitals from 2006 to 2009 indicated that rates of infection may be increasing [4].

The personal, societal, and economic impacts of PJI are significant and include loss of joint mobility, continued disability, and severe financial hardship. A single episode of THA complicated by infection is estimated to have direct costs of approximately $100,000 [5]. A recent Markov analysis projected the total lifetime costs of THA infection to be $389,806 per 65-year-old patient with even higher costs in younger patients; indirect costs such as lost wages, which differentially impact younger patients, accounted for the majority of total costs [6].

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Risk Factors for Prosthetic Joint Infection

Risk factors for PJI can be divided into perioperative, nonmodifiable, and modifiable categories. Perioperative risk factors include antibiotic prophylaxis, surgical site preparation, and control of the operating room environment, which will be discussed in detail in the prevention section.

Nonmodifiable risks include advanced age, higher score on the American Society of Anesthesiologists (ASA) classification of Physical Health Scale, a higher score on the Comprehensive Complication Index (CCI), and certain comorbid medical conditions, such as rheumatoid arthritis, cirrhosis, hepatitis C, and the need for immunosuppressive medications [7–12].

A consensus guideline statement by the American College of Rheumatology and the American Association of Hip and Knee Surgeons (AAHKS) regarding the perioperative management of antirheumatic medications recommended that patients with rheumatic diseases undergoing elective THA or TKA continue nonbiologic, disease-modifying antirheumatic drugs throughout the perioperative period [9]. Another recommendation was for patients to stop biologic medications at least one cycle prior to the surgical procedure and restart them after evidence of wound healing. These recommendations were based mainly on retrospective data [9]. Consideration of these nonmodifiable risk factors is integral to any risk/benefit evaluation prior to surgery.

Modifiable risk factors for PJI include diabetes mellitus, obesity, malnutrition, smoking, human immunodeficiency virus (HIV) infection, and alcohol abuse. Diabetes mellitus establishes a pro-inflammatory state that reduces the body's capacity for healing. A recent meta-analysis of 29 studies found a relative risk for PJI of 1.74 (95% confidence interval [CI] 1.45–2.09) in patients diagnosed with diabetes compared

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_7

to nondiabetic patients [13]. Current research has focused on establishing a hemoglobin A1c (HbA1c) level that is predictive for increased risk of PJI. The American Diabetes Association considers HbA1c >7% as indicating poor glycemic control and many surgeons use this value as a cut-off for performing elective surgeries [14]. A retrospective study of diabetic patients undergoing TJA showed that, while increased HbA1c was associated with increased risk of PJI, most of this risk was not seen until patients exceeded an HbA1c of 7.7% [14]. Therefore, maintaining HbA1c as close to physiologically normal as possible should mitigate most of the increased risk for PJI in diabetic patients.

Obesity is a well-established risk factor for PJI in patients undergoing TJA. A review of US Medicare THA patients between 1998 and 2007 revealed an increased risk of PJI in obese patients, although a precise definition of obesity was not given in this study [15]. A prospective study of 1214 TKA patients found that patents with body mass index (BMI) >40 kg/m^2 had statistically significantly higher odds of developing a deep prosthetic infection [16]. A recent review of modifiable risk factors for PJI suggests consideration of delaying surgery in morbidly obese patients with a BMI >40 kg/m^2, especially in patients with other co-morbid conditions such as uncontrolled diabetes [17].

Bariatric surgical procedures are becoming more common and have been shown to be more effective than nonoperative measures for weight loss in the morbidly obese population [18]. Given the increased risk for postoperative infection in morbidly obese patients, addressing this risk factor with bariatric surgery should lead to decreased risk of PJI, but research has not yet definitively proved this assumption [19, 20]. In fact, Martin et al. reported an increased risk of TKA reoperation in patients who underwent bariatric surgery before arthroplasty, regardless of BMI, compared to patients that did not undergo bariatric surgery [21]. The overall metabolic consequences of bariatric surgery are not fully understood, and further study is needed to clarify their influence on postoperative infection after TJA.

Malnutrition should be assessed and addressed prior to total joint arthroplasty in all patients regardless of BMI, as obese patients are often malnourished [22]. A study by Greene et al. found that patients whose preoperative total lymphocyte count was less than 1,500 cells/mm and whose preoperative albumin level was less than 3.5 g/dL had an increased risk for major wound complications after TJA [23]. Jaberi et al. found that patients requiring surgical debridement for persistent drainage were more likely to be malnourished, as defined by albumin levels <3.5 mg/dL, absolute neutrophil count <1,500, or transferrin levels <200 mg/dL [24]. These data suggest that patients at increased risk for malnutrition may benefit from preoperative screening and, if necessary, consultation with a nutritionist for diet and lifestyle changes.

Smoking has been shown to have deleterious effects on wound healing due to microvascular constriction and decreased oxygen delivery to tissues [25]. A meta-analysis of cohort studies showed a significantly increased risk of PJI (relative risk [RR] = 3.71, 95% CI 1.86–7.41) in patients who were also smokers [26]. In a large retrospective review, Tischler et al. compared the odds of reoperation for infection between current, former, and nonsmokers and found that current smokers were at significantly increased odds for reoperation for infection within 90 days of surgery [27]. Current recommendations include smoking cessation at least 4 weeks prior to elective surgery [17].

The relationship between HIV infection and PJI is less clear. A meta-analysis comparing HIV-infected versus noninfected patients undergoing TJA showed an elevated risk of complications in HIV patients, but authors were not able to specifically analyze the difference in infection rate due to variability in reporting this complication across studies [28]. A retrospective chart review demonstrated that HIV-infected patients undergoing TKA had a significantly higher number of perioperative wound infections; however, the overall complication rate was not significantly different than for non-infected patients [29]. Although there is a lack of definitive data, it appears that patients who have well-controlled HIV have a similar level of risk for PJI as noninfected patients.

Although excessive alcohol use should be avoided due to its overall negative effects on health, its role in risk for PJI in TJA is unclear. A study performed on male patients undergoing major noncardiac surgery showed that patients with an AUDIT-C score (a questionnaire used to gauge heavy drinking) over 5 had significantly more postoperative complications, including infections, compared with nondrinkers [30]. However, a meta-analysis failed to demonstrate a statistically significant increase in risk of PJI in patients that used alcohol [13].

Another risk factor for PJI is preoperative colonization with methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus*. Approximately 20% of healthy persons are persistent carriers of *S. aureus,* and an additional 60% of healthy people are transient carriers [31]. When the current Infectious Diseases Society of America (IDSA) PJI guidelines were drafted, there was not enough evidence to make a recommendation regarding universal decolonization for patients with *S. aureus* colonization [32]. Results of later studies have been mixed. A small trial of screening and decolonization showed little effect on the incidence of surgical site infections and subsequent deep infections [33]. A recent study that instituted a universal screening and decolonization policy found that rates of surgical site infection decreased from 1.11% to 0.34% after implementation [34].

Risk Stratification for PJI

Several PJI risk stratification tools have been developed. The Mayo PJI Risk Score incorporates data such as BMI, previous arthroplasty, previous surgery on the affected joint, immunosuppression, ASA score, and duration of the surgical procedure into a multivariable model that is calculated at baseline and at 1 month post procedure to help determine risk of PJI [35]. A second scoring system, the Readmission Risk Assessment Tool (RRAT), was developed using both modifiable and nonmodifiable risk factors to help determine readmission risk in patients undergoing THA or TKA [36]. None of these risk stratification models have been validated independently.

Organisms Responsible for PJI

A 2014 review that collated the microbiological data from 14 separate studies involving over 2,400 PJI patients found that staphylococcal species was the causative agent in the vast majority of cases [37]. *S. aureus* was found to be present in 27% of the cases, and coagulase-negative staphylococcal species (CoNS) in another 27%. *Streptococci* (8%), *Enterococci* (3%), aerobic Gram-negative bacilli (9%), and *Cutibacterium acnes* (formerly *Propionibacterium acnes*) (4%) were less commonly associated with PJI. Infections were polymicrobial in 15% of cases and culture negative in 14%. Risk factors for polymicrobial infection included age >65, wound drainage and dehiscence after surgery, and rheumatoid arthritis. Other organisms that have been associated with PJI, but at a much lower rate, include *Corynebacteriae*, *Clostridium spp*, *Peptostreptococcus spp*, *Bacteroides fragilis*, and *Actinomyces spp.* Less common organisms associated with PJI include *Mycobacterium tuberculosis* and non-TB mycobacterium, which are more prevalent in immunocompromised individuals. Fungi occur in less <1% of PJIs, with *Candida* species being responsible for approximately 80% of cases. Proposed risk factors for fungal PJI include revision procedure, prior antibiotic use, immunosuppressive therapy, and diabetes mellitus [37].

Clinical Definition of Periprosthetic Joint Infection

Definitive and timely diagnosis of PJI is essential for successful treatment [38]. Currently, there is no single test with conclusive accuracy for diagnosing PJI, so a combination of clinical criteria and testing is necessary for diagnostic confidence [39]. The 2010 American Academy of Orthopaedic Surgeons (AAOS) Guidelines for the diagnosis of periprosthetic joint infections state the diagnosis of PJI should be based on clinical judgement and incorporate information from the patient's history and physical exam, serological testing, synovial fluid analysis, radiographic assessment, and microbiologic and histopathologic testing [40]. These guidelines do not necessarily provide a clear algorithm for PJI diagnosis but stress the importance of obtaining serum inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) prior to aspiration, especially in the setting of chronic infection [40]**.**

In 2011, the Musculoskeletal Infection Society (MSIS) standardized a definition of PJI consisting of major and minor criteria that was revised and widely adopted in 2013 [41]. According to the MSIS definition, PJI can be diagnosed by either one positive major criterion (two positive periprosthetic cultures of phenotypically identical organisms or a sinus tract communicating with the suspect joint) or three of five minor criteria (elevated serum CRP, elevated ESR, elevated synovial fluid white blood cell [WBC] count, elevated synovial fluid polymorphonuclear neutrophil percentage [PMN %)], positive histologic analysis of periprosthetic tissue, and a single positive culture) [42]. A 2018 retrospective study of 182 patients undergoing PJI workup found that the predictive probability of PJI for all 32 combinations of these 5 variables (MSIS minor criteria) was 3.6% for 1 positive variable, 19.3% for 2, 58.7% for 3, 83.8% for 4, and 97.8% for 5, suggesting that the model is highly predictive for identifying PJI [43].

Classification of PJI

In 1996, Tsukayama et al. recommended that the decision to remove or retain the prosthesis be dictated by the clinical setting in which the infection occurred and defined four clinical settings including early postoperative, late chronic, acute hematogenous, and positive intraoperative cultures at the time of revision for presumed aseptic loosening [44]. Early postoperative infections occur within 4–6 weeks of the initial operation and can be treated by irrigation and debridement with retention of implants (see Management section below). Infections identified later than this window are associated with decreased success after attempting debridement with retention and should be treated with staged revision [44]. Chronic infections stem from an indolent infection and are identified more than 4–6 weeks from the time of implantation. The usual clinical scenario is a patient with weeks to months of symptoms, such as wound drainage, swelling, redness, and pain. A prosthesis with a chronic infection must be removed for successful eradication [44, 45].

An acute hematogenous infection consists of the acute onset of symptoms, such as joint pain, swelling, redness, and fever, occurring any time after the early postoperative infection window. If identified promptly, this type of PJI may be

treated similarly to an early postoperative infection with debridement and implant retention [44]. Finally, cases of unexpectedly positive intraoperative cultures at the time of revision for presumed aseptic loosening can be treated with antimicrobial therapy without revision [46].

Established PJI Diagnostic Tests

The exact thresholds for synovial WBC count and PMN % for diagnosing acute and chronic PJI are continually under debate [47]. The 2010 AAOS guidelines describe WBC counts ranging from 1,100 to 3,000 cells/ μL and PMN % >65 as suggestive of chronic PJI [40]. Thresholds for acute PJI vary widely, including 11,200 cells/ μL for acute TKA infections [48], 12,800 cells/μL for acute THA infections [49], and 27,800 cells/ μL for acute TKA infections [50]. It is important to remember that synovial WBC count and PMN % may be unreliable in some scenarios, including corrosion reaction, prior antibiotic use, and traumatic aspiration [51, 52].

Synovial leukocyte esterase (LE), an enzyme produced by activated neutrophils in the setting of infection, is included in standard PJI diagnostic algorithms due to the availability, affordability, and relative ease of testing by dipping a urinalysis strip into synovial fluid [53]. A 2017 study found that synovial LE had the highest test performance for diagnosing PJI compared with serum ESR, serum CRP, synovial WBC, and PMN % [54]. A potential disadvantage of this method is the possibility that blood from a traumatic aspiration can alter the diagnostic color change [53].

As mentioned previously, two positive intraoperative cultures with the same organism are considered diagnostic for PJI whereas one positive culture could be a contaminant and is considered part of the minor criteria [55]. In these cases, cultures must be evaluated in the context of other markers of infection. Culture results have been shown to be primarily helpful in the selection of appropriate antimicrobials and not necessarily the standard reference for diagnosis of PJI due to a large percentage of PJI patients who are culture negative [55].

Novel PJI Diagnostic Tests

While synovial fluid cell count and tissue culture are the mainstays of PJI diagnosis, other tests have been developed in recent decades, including synovial interleukin-6 (IL-6), synovial alpha defensin, serum d-dimer, and DNA sequencing, and are discussed below.

IL-6 is a cytokine produced by activated monocytes and macrophages within the acute inflammatory cascade. Levels of IL-6 rapidly increase in the settings of infection, trauma, and surgery and are highly sensitive and specific for PJI diagnosis [56]. Studies have shown that synovial IL-6 levels below 10,000 pg/ml essentially rule out PJI while IL-6 levels ≥49,000 make the diagnosis of PJI highly likely [57].

The antimicrobial peptide alpha defensin, released into the synovial fluid by inflammatory and endothelial cells in response to microbial products or proinflammatory cytokines, has also been found to be a reliable and accurate biomarker for identifying an infection [58]. However, alpha defensin tends to yield false-positive results in the presence of metallosis and inflammatory or crystalline arthropathies and false-negative results in the presence of low-virulence organisms and is, therefore, generally recommended for use as an adjunct to other testing [58, 59].

D-dimer, a fibrin degradation product released by plasmin secondary to fibrin clot breakdown, is another potential biomarker for PJI. A prospective study of 245 arthroplasty patients showed that serum D-dimer with a threshold of 850 ng/mL demonstrated a high sensitivity and specificity (89.5% and 92.8%, respectively) for PJI diagnosis [54].

Next-generation sequencing (NGS) has been recently investigated as a molecular technology capable of characterizing all microbial DNA present within a given clinical sample. NGS evaluates databases for any bacteria, virus, yeast, fungi, and parasite match and can, therefore, be used to analyze synovial fluid and/or tissue [60]. This technology also can determine antibiotic resistance based on identification of resistance genes within the sample [60]. Although powerful, this method's overall cost and potential for DNA contamination present significant challenges [60].

In conclusion, the diagnosis of PJI is challenging and may be uncertain in clinically ambiguous presentations. Emerging biomarkers and novel techniques may serve as useful adjuncts in improving the diagnostic accuracy of PJI. Further research may yield better guidelines for application of these tests and improve clinical utility.

Management

Once a PJI has been diagnosed, there are multiple treatment strategies depending on the timing of the infection, organism, patient comorbidities, and implant factors. The main treatment methods are discussed below, including debridement, antibiotics, and implant retention (DAIR); single-stage revision; two-stage revision; salvage procedures; and antibiotic suppression. Table 7.1 contains an overview of the main antimicrobials used to treat the most common organisms involved in PJI as recommended by the IDSA.

Table 7.1 IDSA recommendations for antibiotic treatment of various organisms [32]

Organism	Recommended antimicrobial
Methicillin-susceptible *Staphylococcus*	Nafcillin, cefazolin, ceftriaxone
Methicillin-resistant *Staphylococcus*	Vancomycin
Enterococcus	Penicillin G, ampicillin
Penicillin-resistant *Enterococcus*	Vancomycin
Pseudomonas aeruginosa	Cefepime, meropenem
Enterobacter	Cefepime, ertapenem
β-Hemolytic streptococci	Penicillin G, ceftriaxone

Debridement, Antibiotics, and Implant Retention (DAIR)

DAIR involves operative debridement of infected tissue including exchanging any readily removable prosthetic material, such as the femoral head component and polyethylene liner in the case of THA, and the polyethylene tibial insert in the case of TKA. The implanted metal components are retained. Intraoperative cultures are sent to help direct treatment, and a course of antibiotics ranging from 2 to 6 weeks, depending on clinician preferences and organism, is begun following the procedure [37]. DAIR is indicated for acute infections, but the exact definition of "acute" is debatable with recommendations ranging from symptom onset within 3 weeks to up to 12 weeks from the initial procedure [32, 37, 61, 62]. It is important to include late acute hematogenous infections with symptoms present for less than 3 weeks in these indications [37].

DAIR is a faster and less costly procedure with lower morbidity compared with a single- or two-stage revision procedure involving implant explantation (which may be especially relevant for elderly patients with multiple medical comorbidities) [61]. The main disadvantage of DAIR is its reduced effectiveness in eradicating infection compared with implant explantation [63]. Reported success rates of DAIR for THA and TKA vary from 30% to 80%; individual studies often employ variable clinical selection criteria for DAIR patients and definitions of success and failure [37, 62–64]. Failed DAIR may lead to higher failure rates and lower functional outcomes following subsequent two-stage revision [65].

A promising line of research aims to identify predictors of DAIR failure to help clinicians make an informed decision regarding the appropriateness of DAIR versus staged revision. Potentially predictive factors include high inflammatory markers, arthroscopic debridement (as opposed to reopening the prior incision), MRSA infection, presence of a sinus tract, longer duration of symptoms, presence of a cemented prosthesis, nicotine use, and certain medical comorbidities [37, 62, 64].

Single-Stage Revision

Single-stage revision for PJI involves explantation of all components, debridement of infected tissue, and reimplantation of revision arthroplasty components in a single procedure, followed by antibiotic treatment. The reimplantation portion of the procedure involves new surgical equipment, instruments, and draping to avoid contamination [66]. It is more commonly performed in Europe than in the US where two-stage revision is preferred [37, 66]. Single-stage revision is indicated for chronic infections in patients with adequate bone stock and soft tissue envelope, preoperatively identified nonvirulent and nonresistant organisms, and for acute infections in patients with a high risk of failing DAIR (see above) [66, 67].

Advantages of single-stage revision compared with two-stage revision include fewer procedures leading to decreased patient morbidity and reduced cost, as well as potentially improved functional outcomes [66–68]. Disadvantages include a longer operative time within a single procedure and limited indications [66]. Results of single-stage revision are better than those associated with DAIR; systematic reviews from the past 5 years have reported single-stage revision reinfection rates of 16.8% [68] and 7.6% [13]. Whether the noninferiority or superiority of single-stage versus two-stage revision can be convincingly proven remains an open question.

Two-Stage Revision

Two-stage revision involves an initial procedure with explantation of all components and placement of an antibiotic cement spacer, followed by a 4- to 6-week period of antibiotic treatment [37]. After the conclusion of the treatment course, patients have an "antibiotic holiday" during which they are monitored for any signs of continued infection, including wound appearance, inflammatory markers, and repeat joint aspiration [37]. If the infection is thought to have resolved, the second-stage procedure, in which the spacer is removed and permanent revision implants are inserted, is performed. If the infection is not resolved, a repeat debridement and antibiotic spacer is usually performed and the process is repeated.

There may be a limited role for what can be called a "partial two-stage revision" in the case of an infected THA with a well-fixed femoral stem where stem removal would lead to femoral bone loss and increased patient morbidity. This involves open debridement, removal of the acetabular component, retention of the femoral stem, and placement of a femoral head component made from antibiotic cement molded in a bulb syringe (Fig. 7.1) [69]. A single study of this method found a 4-year reinfection rate of 11% [69].

In the US, two-stage revision is considered the "gold standard" for treatment of chronic PJI or acute infections in patients with a high risk of failing DAIR [13]. This procedure has the advantage of a history of relatively low reinfection rates and applicability in nearly every case of PJI as long as the patient is able to withstand the two surgical procedures; the disadvantages of increased morbidity and high cost are discussed above [13, 67]. Results of two-stage revision, as with single-stage revision, are improved compared with DAIR, with a wide range of reported success rates generally around 80–100% [13]. One study reported that patients who required an interim spacer exchange (i.e., were found to have an unresolved infection after the initial first stage of the revision) had a lower 5-year infection-free survival rate compared with those who did not require an interim spacer exchange [70]. The body of literature is significantly larger for two-stage compared with single-stage revisions [13], and there are no results from randomized clinical trials comparing the two methods, although the protocol for a randomized study comparing one-stage versus two-stage revisions for infected THA has been published (INFORM trial) [71].

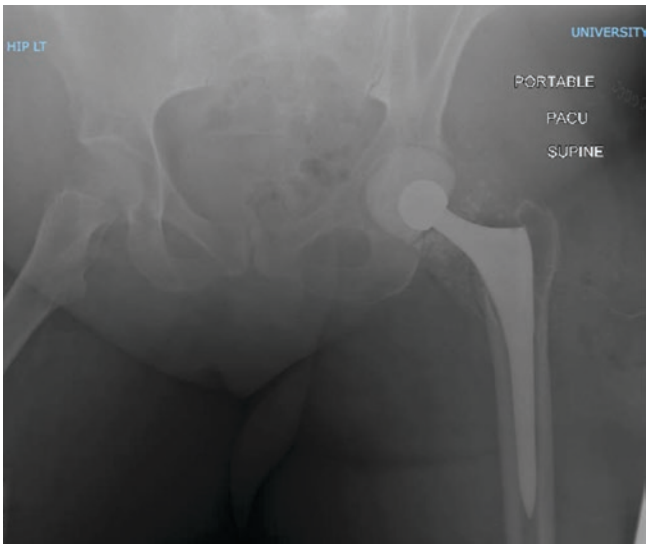

Fig. 7.1 Partial two-stage hip revision with a retained femoral stem and antibiotic cement femoral head

There are many controversies in the orthopaedic surgery and infectious disease literature surrounding various aspects of the two-stage revision process. In the case of TKA, debate exists regarding the use of a static spacer (Fig. 7.2) versus a dynamic or articulating spacer (Fig. 7.3) [72].

There are no definitive data at this point regarding the superiority of either method [72–74]. There is also no consensus regarding the duration of the antibiotic holiday and the best method for determining whether the infection is resolved between the two stages [75]. Finally, while frozen sections have been recommended traditionally as part of the

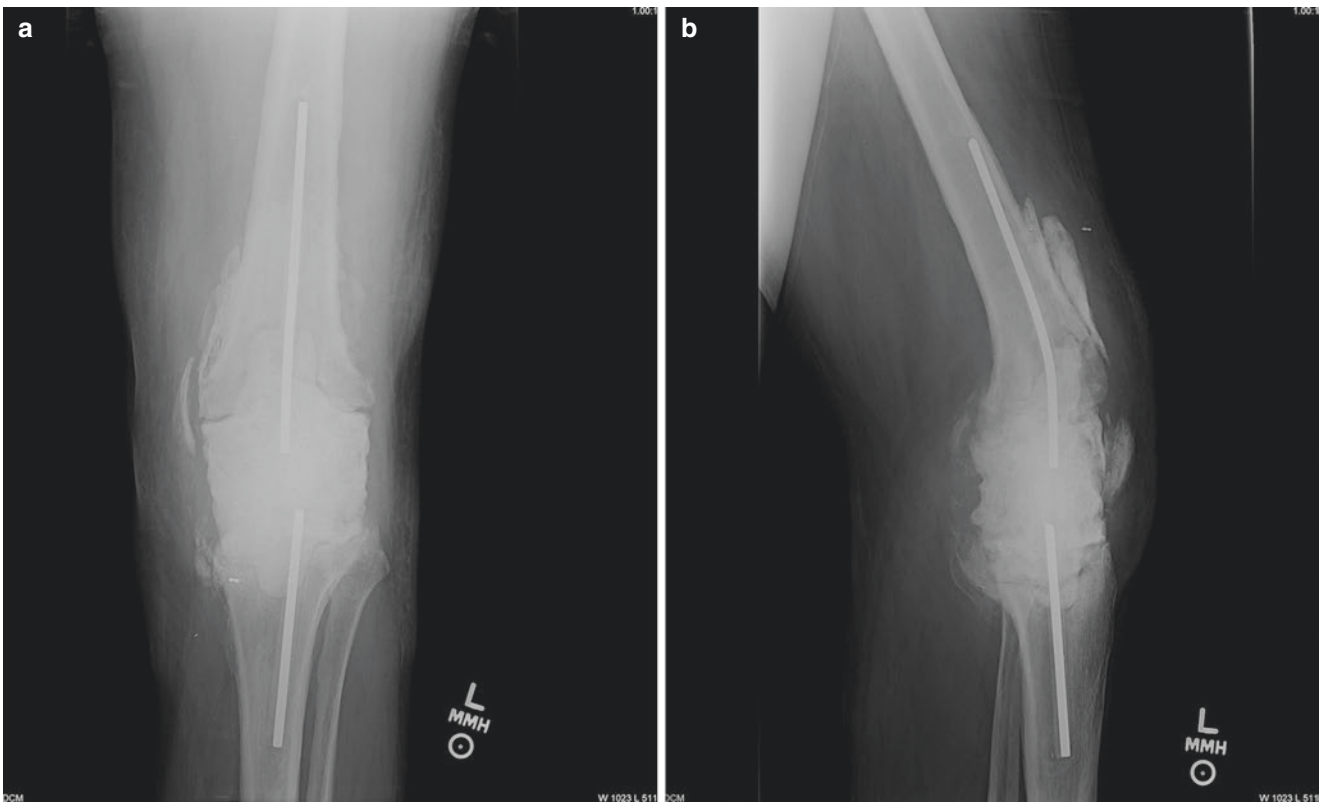

Fig. 7.2 A static spacer for a two-stage knee revision, AP (**a**) and lateral (**b**) views

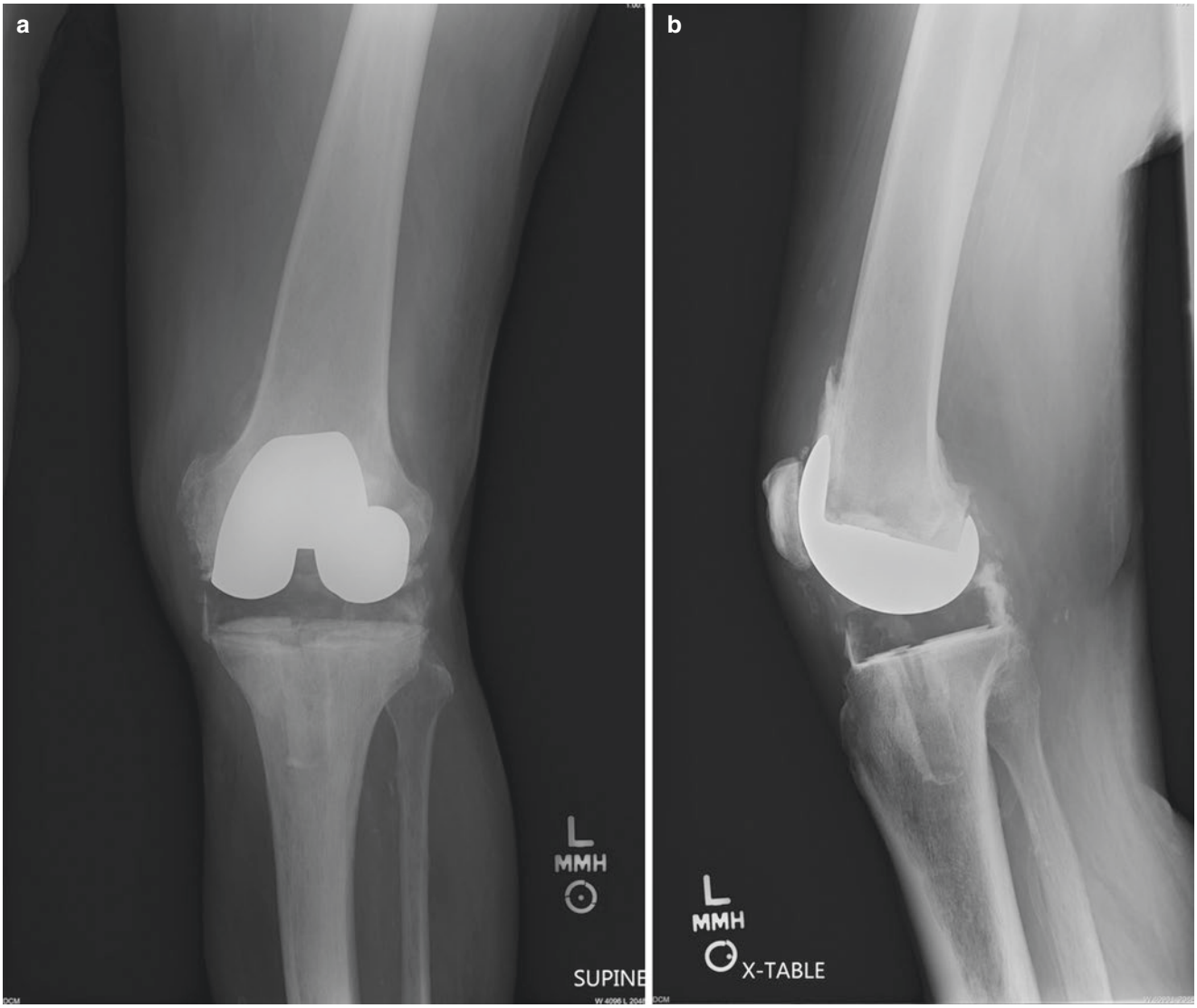

Fig. 7.3 Dynamic or articulating spacer for a two-stage knee revision, AP (**a**) and lateral (**b**) views

second-stage procedure to ensure that infection is eradicated, 2010 AAOS guidelines recommend using frozen sections only in patients for whom the diagnosis of PJI has not been definitively established or excluded [37, 76].

Salvage Procedures

A salvage procedure may be indicated in the case of failed one- or two-stage revision procedures for PJI, or in patients who are unable to withstand the morbidity of revision procedures. Recurrent infection of a THA may be addressed by resection arthroplasty, which involves removal of the acetabular and femoral components as definitive treatment without the placement of a cement spacer [77, 78]. This procedure allows for treatment of the infection while avoiding amputation, although patients will have limited mobility and generally need a walking aid [78]. For persistent TKA infection, salvage consists of arthrodesis (knee fusion), which can be done using an intramedullary nail, plate fixation, or an external fixator [79]. Failure of these procedures, either by persistent infection or nonunion in the case of knee arthrodesis, may necessitate above-knee amputation.

Antibiotic Suppression

Chronic antibiotic suppression has a role in the treatment of PJI [77, 80]. Chronic suppression has been used in patients with multiple medical comorbidities and continued PJI after multiple revision attempts who wish to avoid amputation, as well as preventatively following operative

treatment [77, 80]. A 2015 study by Siquiera et al. found that patients who received chronic antibiotic suppression with oral antibiotics after DAIR or two-stage revision had a statistically significant higher 5-year infection-free prosthetic survival rate than patients who did not receive chronic antibiotic suppression [80]. Despite these encouraging findings, the risk of side effects from long-term oral antibiotic administration and the potential contribution to the emergence of multidrug-resistant organisms should be considered [81].

Prevention

Modifiable Patient Risk Factors

One method of preventing PJI is to address modifiable patient risk factors before the procedure takes place. As discussed above, poor diabetes control, obesity, smoking, alcohol use, malnutrition, and HIV infection have been shown to affect PJI risk. Surgeons can attempt to mitigate PJI risk by implementing cut-offs for HbA1c and BMI; advising patients to quit smoking at least 4 weeks pre-operatively and to minimize alcohol use; screening total lymphocyte, albumin, and/or prealbumin levels; and monitoring HIV viral load and CD4 counts in infected patients.

Perioperative Risk Factors

Several factors that play a role in the prevention of infection are under the surgeon's control, including use of perioperative antibiotics, surgical site preparation, surgical attire, and operating room conditions.

Studies have found that administration of perioperative antibiotics decreases the risk of wound infection in both primary and revision arthroplasty procedures [82]. Multiple guidelines have been published regarding the selection and timing of antibiotic administration. The 2005 Surgical Infection Prevention Guideline Writers Workgroup recommends cefazolin or cefuroxime as prophylaxis for hip and knee arthroplasty, with vancomycin or clindamycin recommended in cases of confirmed beta lactam allergy and vancomycin recommended in the case of MRSA colonization [83]. The group also recommends initiating the first dose of antibiotic within 60 minutes of surgical incision and discontinuation of antibiotics within 24 hours of surgery completion [83]. The 2017 Center for Disease Control and Prevention (CDC) guidelines recommend a single dose of preoperative prophylactic antibiotics without additional postoperative dosing [84]. In 2018, the AAHKS Evidenced-Based Medicine Committee stated that they disagree with the CDC guidelines and recommend 24-hour postoperative antibiotic prophylaxis pending further research [85].

Surgical site preparation plays a role in the reduction of postoperative infection. Hair surrounding the planned incision site should be trimmed close to the time of incision with trimmers as mechanical razors may lead to bacterial colonization by causing injury to the skin. The optimal skin preparation agent has yet to be determined, and there is evidence supporting the use of both iodine-based and chlorhexidine solutions [86, 87]. Johnson et al. demonstrated that use of chlorhexidine-impregnated cloths the night before and morning of surgery yielded a statistically significantly lower incidence of surgical site infections after TKA [88].

Surgical exhaust suits are commonly used in arthroplasty procedures with the intent to reduce wound contamination. Although some studies have found that use of these suits leads to a decrease in colony-forming units in the field, others have found no difference in wound contamination between use of body-exhaust suits versus standard occlusive gowns [89, 90].

Surgical gloves have been identified as a source of potential contamination. A 1981 study by McCue et al. cultured inner and outer gloves following THA procedures and found that outer gloves used exclusively for draping were the most frequently contaminated, leading them to recommend changing outer gloves routinely after draping [91]. Al-Maiyah et al. compared glove contamination during procedures in which outer gloves were changed every 20 minutes versus gloves that were kept in place until cementation [92]. The less frequently changed gloves were more contaminated, leading to a recommendation of frequent glove changes to limit wound contamination [92].

Operating room conditions have been studied extensively to identify potentially modifiable risk factors for infection. Operating rooms with laminar air flow have been proposed to limit wound contamination although the results of studies examining bacterial contamination in such rooms are conflicted [89, 93–95]. Limiting operating room traffic during the procedure seems to reduce wound contamination [89]. Rezapoor et al. found that both the number of personnel in the operating room and the number of door openings per minute correlated with an increased density of airborne particles in the operating room [96].

Conclusion

To prevent the occurrence of PJIs after TJA, the surgeon must be cognizant of all factors that play a role in pathogenesis. By mitigating both patient and operating room-related modifiable risk factors, surgeons can optimize their risk profile and minimize costly infectious complications.

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Opportunistic Infections Associated with Biologic Therapy

8

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Introduction

By the end of the twentieth century (1998), the antitumor necrosis factor (TNF) monoclonal antibody infliximab, and the fusion protein that binds TNFα, etanercept, which aimed to treat rheumatoid arthritis (RA) and other rheumatic/autoimmune conditions, were launched. Soon after, other TNF inhibitors (TNFis) and biologics targeting other cytokines or with a different mechanism of action were also approved to treat not only RA but also other rheumatic/autoimmune conditions. In rheumatic/autoimmune disorders, among which the most representative is RA, mortality and infections, in particular, are increased compared with the general population [1]. Leading causes are the inherent characteristics of autoimmune disorders, associated comorbidities, and drugs used for treatment, such as glucocorticoids, conventional disease-modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs), and immunosuppressive agents [1–3]. Along these lines, glucocorticoids are especially relevant, given most patients are either intermittently or chronically receiving this drug, and their risk of infection rises exponentially as long as the doses are increased [2]. Both cDMARDs and bDMARDs can serve as corticosteroid-sparing agents and can improve disease control.

Nonetheless, higher infection rates among TNFi users have generally been observed [3], and a moderate increase in hospitalizations for infections in the first year of treatment with TNFis has been reported [4]. This risk has been observed in both randomized clinical trials and registries [5]. However, a better knowledge of these drugs and almost two decades of clinical experience of them have led to the implementation of preventive measures that have proven to be useful in preventing the most severe or frequent infections.

Opportunistic infections (OIs) can emerge in individuals in several circumstances, especially in those with autoimmune disorders in whom immunologic surveillance is altered or compromised, and when the patient is treated with immunosuppressive agents. As Bryant et al. [6] mentioned in their review, the definition of what could be considered an OI has not been unanimous. In 2009, Kaplan et al. [7] defined OI for patients infected with HIV as infections that are more frequent or more severe because of immunosuppression. However, this definition is ambiguous and includes any infection triggered by any pathogen, which would lead to interpreting as an OI any infectious situation originating from any pathogen. To clarify this situation, a group of recognized researchers [8] published an evidence-driven consensus document in which, rather than establishing a definition of what should be considered an OI, they developed and ratified a list of pathogens that should be regarded as OI in the setting of targeted therapies. Twenty-four pathogens and/or presentations of specific pathogens were identified as definite OI and 11 as probable OI. This list should be considered a potential indicator of alterations in host immunity [8].

Opportunistic Infections with Biologics

Most of the accumulated experience with bDMARDs arises from TNFis. These drugs have been used for 20 years to treat rheumatic conditions including RA, inflammatory bowel diseases (IBDs) (especially Crohn's disease [CD]), and cutaneous diseases (psoriasis).

Several studies have shown an increase in OI in patients treated with biologics, especially TNFis. Data from biologics other than TNFis are more limited. Thus, in patients with CD who have received steroids, immunosuppressive therapy, or TNFis, Marehbian et al. [9] demonstrated an increased risk of tuberculosis (hazard ratio [HR] 2.7; 95% confidence interval [CI], 1.0–7.3), candidiasis (HR 2.7; 95% CI, 1.8–

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_8

4.0), and herpes zoster (HR 1.7; 95% CI, 1.0–2.7), compared with CD controls. The use of two or three of these medications further increased the risk. Similar results were found in another study in patients with CD [10].

The United States Safety Assessment of Biologic Therapy (SABER) study found a higher rate of nonviral OIs among a cohort of new users of TNFis (RA, IBD, psoriasis, psoriatic arthritis [PsA] and ankylosing spondylitis [AS]) versus those initiating therapy with cDMARDs. Pneumocystis was the most frequent pathogen involved, and in patients with RA, rates of OI in new users of infliximab were higher than those produced in new users of cDMARDs and etanercept [11]. A retrospective study based in Spain that only analyzed patients treated with infliximab in several diseases showed a significantly higher risk of OI in the first year of treatment (odds ratio [OR] 8; 95% CI 2–50); the most frequent OI was tuberculosis in four of nine cases [12]. A one-year Japanese prospective study aimed at detecting OI involved 570 patients. The design was a case-control study in which two noninfected patients with IBD were selected as controls for each case. Fifty-two (9.1%) of 570 patients with IBD had an OI, with *herpes simplex virus* and *herpes zoster* (HZ) *virus* infections being observed in 29 and 16 patients, respectively. No cases of active tuberculosis were detected; steroids, thiopurine, and immunosuppressive therapy significantly increased the rate of OI ($p = 0.02$, $p < 0.01$, and $p < 0.01$, respectively). However, infliximab did not increase the incidence of OI ($p = 0.62$) [13]. French investigators analyzed the RATIO register and focused on OI occurring in patients receiving several TNFis for rheumatic conditions, psoriasis, and IBD; tuberculosis cases were excluded. The design was a case-control study with three controls treated per case. Forty-five OIs were registered in 43 patients. One-third (33%) had bacterial infections (four listeriosis, four nocardiosis, four atypical mycobacteriosis, three nontyphoid salmonellosis) and 40% were viral, mainly HZ. Infliximab (OR 17.6; 95% CI 4.3–72.9; $p < 0.0001$) and adalimumab (OR 10.0; 95% CI 2.3–44.4; $p = 0.002$) had an increased risk compared with etanercept. Other factors that increased the risk of OIs were steroids at doses over 10 mg/day [14].

Current evidence of OI in patients receiving biologics is classified according to the type of microorganism:

- *Bacterial infections*
  - Mycobacteria
    - Tuberculosis
    - Nontuberculous mycobacteria
  - Other: listeriosis, legionellosis, and nocardiosis
- *Fungal infections*
  - Pneumocystosis
  - Histoplasmosis
  - Coccidioidomycosis
- *Viral infections*
  - Varicella-zoster virus
  - Cytomegalovirus
  - Progressive multifocal leukoencephalopathy (PML): The John Cunningham virus (JCV)
  - Hepatitis virus

Bacterial Infections (See Table 8.1)

Tuberculosis

The role that TNF-α plays in the host defense against tuberculosis, including granuloma formation, could explain the tuberculosis cases that appeared after treating patients with TNFis. In 2001, Keane et al. [15] reported 70 cases of tuberculosis after treatment with infliximab (67% RA and 26% CD) for a median of 12 weeks. In 48 patients, tuberculosis developed after three or fewer infusions, and 40 of the patients had an extrapulmonary disease. Afterward, the Spanish Society of Rheumatology published the data included in the Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases database, BIOBADASER. Seventeen cases of tuberculosis (16 RA and 1 PsA) were reported, 7 of 17 with disseminated tuberculosis. The estimated incidence of tuberculosis associated with infliximab was 1,893 cases per 100,000 patients in the year 2000 and 1,113 cases per 100,000 patients in the year 2001. Tuberculosis incidence in Spain in the year 2000 was 21 cases per 100,000 inhabitants [16]. The same group demonstrated for the first time that implementing the official recommendations to screen and treat latent tuberculosis were useful in preventing tuberculosis in patients treated with TNFis. Rates of tuberculosis decreased by 78% (incidence rate ratio [IRR] 0.22; 95% CI 0.03–0.88; $p = 0.008$), whereas among patients with RA the rate dropped by 83% and reached the rates of RA treated with cDMARDs (IRR 1.0; 95% CI 0.02–8.2) [34]. Interestingly, the probability of developing tuberculosis was seven times higher when recommendations were not followed (IRR 7.09; 95% CI 1.60–64.69) [17]. The increased risk of developing tuberculosis with TNFis has also been demonstrated in other studies from around the world [18–22].

A few studies comparing the incidence of tuberculosis between infliximab, adalimumab, and etanercept showed that monoclonal antibodies (infliximab and adalimumab) led to a higher risk of developing tuberculosis than the TNFi receptor etanercept. Thus, Tubach et al. [23] collected 69 cases of tuberculosis in patients with rheumatic diseases, cutaneous diseases, and IBDs in the French RATIO register. The tuberculosis standardized incidence ratio (SIR) compared with the French population was 12.2 (95% CI 9.7–15.5) and was higher for therapy with infliximab and adalimumab than for etanercept: SIR 18.6 (95% CI 13.4–25.8) and SIR 29.3 (95% CI 20.3–42.4) versus SIR 1.8 (95%

Table 8.1 Opportunistic bacterial infections in patients treated with biological drugs

Author	Type of study	N° of patients	Treatments	Time of follow-up	Pathology	Incidence/risk/%
Bacterial infections						
Tuberculosis						
Keane et al. 2001 [15]	Case reports	70 with TBC	Infliximab	12 weeks	RA CD JIA AS BD	IR: 6.2 cases/100,000 pt/year
Gómez-Reino et al. 2003 [16]	Registry (BIOBADASER)	1,540 (17 with TBC)	Infliximab	2 years (2000 and 2001)	RA	IR:1.9 cases /100,000 pt/year (2000) IR:1.1 cases/100,000 pt/year (2001)
Gómez Reino et al. 2007 [17]	Registry (BIOBADASER)	5,198 (15 with TBC)	TNFis	4 years (2002–2006)	RDs	IR:172/100,000 pt/year
Wolfe et al. 2004 [18]	Registry (NDB)	6,460	Infliximab	2 years (2000–2002)	RA	IR: 52.5 cases/100,000 pt/year
Askling et al. 2005 [19]	Registry	36,115 (33 with TBC)	TNFis	2 years (1999–2001)	RA	RR: 2 (1.2–3.4) in RA (without TNFis) RR: 4 (1.3–12) in RA (with TNFis)
Sichletidis et al. 2006 [20]	Retrospective study	613 (11 with TBC)	TNFis	4 years (2000–2004)	RDs	IR:449 cases/100,000 pt/year
Brassard et al. 2006 [21]	Cohort	112,300 (386 with TBC)	Biologics cDMARDs	5 years (1998–2003)	RA	IR: 2.2 cases/1000 pt/year (All) IR: 2.6 cases/1000 pt/year (Biologics)
Yoo et al. 2014 [22]	Retrospective study	175 (3 with TBC)	TNFis	6 years (2005–2011)	ICDs	IR: 77.7 cases/1000 pt/year
Tubach et al. 2009 [23]	Case and control	69 with TBC	TNFis	3 years (2004–2007)	RDs	IR: 117 cases/100,000 pt/year
Dixon et al. 2009 [24]	Prospective study	13,944 (40 with TBC)	TNFis cDMARDs	7 years (2001–2008)	RA	IR: 118 cases/100,000 pt/year (TNFis)
Rutherford et al. 2018 [25]	Registry (BSRBR)	19,282	Biologics	13 years (2002–2015)	RA	IR: 55 cases/100,000 pt/year
Arkema et al. 2015 [26]	Registry (SRQ)	175,972 (43 with TBC)	Biologics cDMARDs	9 years (2002–2011)	RA	HR: 4.4 (2.3–8.5) (All) HR: 4.2 (2.7–6.7) (cDMARDs) HR: 7.4 (3.3–18.9) (Biologics 2002–2006) HR: 2.4 (0.9–6.1) (Biologics 2007–2011)
Nontuberculous mycobacteria						
Winthrop et al. 2013 [27]	Cohort	8418 (18 with NTM)	TNFis	8 years (2000–2008)	RDs	IR: 74 cases /100,000 pt/year
Lee et al. 2013 [28]	Cohort	509 (4 with NTM)	TNFis	9 years (2002–2011)	RDs	IR: 231 cases/100.000 pt/year
Listeriosis						
Slifman et al. 2003 [29]	Case reports	15 with Listeriosis	TNFis	3 years (1998–2001)	RA CD	IR: 43 cases/1000,000 pt/year
Peña-Sagredo et al. 2008 [30]	Case reports	6 with Listeriosis	TNFis	6 years (2001–2007)	RDs	IR: 0.256 cases /1000 pt/year
Davies et al. 2013 [31]	Cohort	11,723 (9 with Listeriosis)	TNFis	9 years (2002–2011)	RA	IR: 5.1 cases/10,000 pt/year (before 2006) IR: 1.4 cases/10,000 pt/year (after 2006)
Legionellosis						
Tubach et al. 2006 [32]	Registry (RATIO)	10 with Legionellosis	TNFis	1 year (2004)	ICDs	RR: 16.5–21 cases/100,000 pt/year
Nocardiosis						
Ali et al. 2013 [33]	Review of case reports	7 with Nocardiosis	TNFis	—	ICDs	—

TBC tuberculosis, *NTM* nontuberculosis mycobacteria, *RA* rheumatoid arthritis, *CD* Crohn's disease, *JIA* juvenile idiopathic arthritis, *AS* ankylosing spondylitis, *BD* Behcet disease, *ICDs* inflammatory chronic diseases, *RDs* rheumatic diseases, *TNFis* tumour necrosis factor inhibitors, *cDMARDs* conventional disease-modifying antirheumatic drugs, *IR* incidence rate, *HR* hazard ratio, *RR* relative risk, *pt* patient

CI 0.7–4.3), respectively. Similar results were found in the British Society of Rheumatology Biologics Register (BSRBR) and the Swedish register [24–26]. These findings can be explained by differences in the action of the two types of agents on membrane-bound TNF [23]. It is important to note that the lower rate with etanercept compared with the other TNFis does not mean there is a negligible risk with this drug. Although relatively safer than the monoclonal antibodies, clinicians should be aware that etanercept still confers an increased risk for tuberculosis [23, 24].

Furthermore, a recent review of OI in the British register found that the incidence of tuberculosis was significantly lower in patients treated with rituximab than with a TNFi, with 12 cases recorded per 100,000 patient years compared with 65 cases per 100,000 patient years. Similar findings were found when tocilizumab data were analyzed; the adjusted HR of rituximab compared with TNFis was 0.96 (95% CI 0.62–1.50), and 0.52 (95% CI 0.17–1.65) compared with tocilizumab [25]. Hence, it has been suggested that tuberculosis is a class effect of TNFis. In fact, some reviews found that the risk of tuberculosis with non-TNFis was negligible, raising the question of whether the screening procedures for latent tuberculosis would then be necessary in those cases in which patients are treated with non-TNFi drugs [35, 36]. However, we encourage caution and performance of the screening procedure for any patient treated with biologics or for patients who are immunosuppressed and are at risk of developing tuberculosis.

Detecting latent tuberculosis before initiating TNFi treatment is crucial to preventing the development of tuberculosis. Furthermore, screening measures and treatment with isoniazid have been demonstrated to be highly effective in preventing the development of tuberculosis in patients treated with TNFis. Because the epidemiological situation of tuberculosis varies around the globe, measures to prevent this infection must follow the national recommendations of each country [34, 35, 37, 38]. In some countries, a chest X-ray and a tuberculin skin test (TST) (positive ≥5 mm) have been shown to be useful in screening for latent tuberculosis [34]. However, most recommendations have incorporated the use of interferon (INF)-γ release assays. They are helpful in patients with a history of previous Bacillus Calmette–Guérin vaccination because a TST test could produce a false-positive result. Nonetheless, we should remember that INF-γ release assays and TST might also produce false-negative results, especially in immunosuppressed patients [39].

Nontuberculous Mycobacterial Disease

Nontuberculous mycobacteria (NTM) infection appears to be increasing in some countries, especially in those such as the USA, where tuberculosis has a low prevalence [3, 27, 40]. A survey conducted in 2007 of the members of the Infectious Diseases Society of America Emerging Infections Network reported a total of 1876 mycobacterial infections occurring in the previous 6 months: 1021 (54%) were NTM infections and 855 (46%) were tuberculosis; all cases occurred in Canada and the USA. Of these infections, 49 were associated with the administration of biologics (infliximab, etanercept, adalimumab, or rituximab) of which 32 were NTM infections and 17 tuberculosis; these figures represent NTM infection almost twice as high [40]. NTM infection is more difficult to diagnose because, in general, it is more insidious in its onset and progression, which could explain the reason for the underreporting of cases [40]. NTM infection is also more prevalent in women, especially in those older than 50 years [41, 42]. The electronic records of Kaiser Permanente Northern California [27] were searched for patients treated with a TNFi who had developed tuberculosis or an NTM infection. Of the 8,418 TNFi users, 18 developed NTM and 16 tuberculosis after commencing treatment. TNFi-associated rates of NTM were 74 (95% CI 37–111) per 100,000 person-years. Background rates for NTM in unexposed patients with RA were 19.2 (95% CI 14.2–25.0) and in the general population 4.1 (95% CI 3.9–4.4) per 100,000 person-years. In this study, more patients with NTM died compared with patients with tuberculosis; OR 14.4 (95% CI 4.7–40.8) versus OR 5.2 (95% CI 1.0–19.1). However, various factors might have an impact on the results, mainly the difficulty in treating NTM disease. Finally, the authors stated that due to the methodology of the study they could not conclude that anti-TNF drugs independently increased the risk for NTM [27]. Another study conducted in South Korea showed an increase of NTM infection in patients treated with TNFis. The estimated NTM incidence was 230.7 per 100,000 patients per year [28].

Unfortunately, there are no guidelines to screen for NTM disease; therefore, more studies focus on preventing, diagnosing, and treating this disease are warranted.

Other Bacteria

Listeriosis

Infection by *Listeria monocytogenes* (LM) is linked to treatment with TNFis, given TNFα plays a pivotal role in the control of intracellular bacterial infection [43]. The United States Food and Drug Administration (FDA) Adverse Event Reporting System was reviewed through December 2001 and 15 cases were found, including six deaths, of LM infection associated with infliximab (14) or etanercept (1) treatment. Nine cases had RA and six cases CD [29]. A search in the BIOBADASER register found an incidence of LM infection of 0.256 per 1,000 patient-years (95% CI 0.115–0.570) in patients with rheumatic conditions treated with TNFi. Compared with the incidence rate in the general population

from Europe (0.0034 per 1,000 person-years), the IRR of LM infection for patients treated with TNFis was 75.3 (95% CI 33.8–168.0); $p < 0.001$ [30]. A recent publication focused on the BSRBR showed that when patients were provided with informative leaflets on TNFi, with advice to avoid high-risk foods such as raw eggs and poultry, the incidence of new listeria and salmonella infections dropped dramatically [31].

Legionellosis

Legionellosis often presents as pneumonia and is mainly caused by *Legionellosis pneumophila* serogroup 1, a ubiquitous, opportunistic, Gram-negative intracellular pathogen [32]. The RATIO register in France reported 10 consecutive cases of this pneumonia in patients who were treated with infliximab, etanercept, or adalimumab. Most patients were receiving steroids, and six had concomitant treatment with methotrexate. No patient died. The authors estimated an increased risk of legionellosis compared with the general population in France of 16.5–21, although they admitted that this figure could be biased because, as usual, incidence rates might be "underestimated or overestimated because of imprecise figures in the denominator or numerator"[32].

Nocardiosis

Nocardia species are Gram-positive bacteria found in soil and water that can affect the lungs, brain, and skin in immunocompromised patients [33].

In 2013, Ali et al. [33] published one original case and included seven additional cases, after a review of the literature, of nocardiosis in patients with IBD, RA, or psoriasis treated with TNFis (adalimumab or infliximab). All the patients, except one who died, survived after withdrawing TNFi and receiving the appropriate treatment. Concomitant therapy with immunosuppressive agents and/or corticosteroids had been administered to all eight patients.

Fungal Infections (See Table 8.2)

Pneumocystosis

Pneumocystis jirovecii is a fungus that was recognized as a cause of OI; first, in patients with congenital immunodeficiencies, in immunosuppressive therapies for cancer, and in AIDS [55]. Further reports described cases of *Pneumocystis jirovecii* pneumonia (PJP), in patients with RA treated with low doses of methotrexate or in autoimmune disorders and Wegener's granulomatosis [56–58]. Once biologics were on the market, several cases of pneumocystis infection were reported in patients treated with TNFis. Five cases of PJP were reported in 57,711 French patients in the RATIO register with various autoimmune disorders [14]. On the other hand, in the SABER study, focused on nonviral opportunistic infections, 16 cases of pneumocystosis were reported in a cohort of 33,324 new users of TNFi [11]. Postmarketing surveillance in Japan identified 22 cases of PJP after a follow-up of 6 months of 5,000 patients receiving infliximab [44]. A similar Japanese study, but using etanercept, found 16 cases of PJP among 102 patients with pneumonia in 7,091 patients with RA followed for 6 months [45]. A review of the FDA Adverse Event Reporting System for cases of *Pneumocystis* infection associated with infliximab-use from January 1998 through December 2003 found 84 cases of PJP with infliximab. Most cases were in patients with RA or CD, 49 and 14, respectively. Methotrexate and prednisone were the most frequent concomitant therapy [46]. Despite these findings, whether or not biologic therapy increases the risk of PJP is still debatable. A study performed in the USA analyzed the trend in hospitalizations for PJP among patients with RA from 1996 to 2007. The findings indicated that changes in the occurrence of PJP associated with the use of immunosuppressive and biologic agents were not detectable over the background occurrence [59]. Another study in the UK compared the risk of PJP in patients with RA treated with TNFi (13,905 patients) with that in patients with RA treated only with cDMARDs (3,677 patients). Data from the BSRBR were used. Seventeen cases were considered definite or probable infections: 15 with a TNFi (14 receiving drug and 1 with past TNFi exposure) and 2 with a standard DMARD. The findings showed a small absolute risk for PJP with incident rates of 2.0/10,000 person-years' follow-up (95% CI 1.2–3.3) and 1.1/10,000 person-years' follow-up (95% CI 0.3–4.3) in the TNFi and cDMARD cohorts, respectively. The median time to PJP infection was 5.8 months (interquartile range 2.7–16.8) after starting TNFi. The authors concluded that PJP is a rare infection and that the data did not allow establishing a definitive risk of increased PJP in patients with RA treated with TNFis [47].

Furthermore, a recent publication that analyzed OI in the same database (BSRBR) showed that the overall incidence of OI was not significantly different among different biologic classes. Male sex, age, and comorbidity were the strongest predictors of OI. However, the rate of *Pneumocystis* infection was significantly higher with rituximab than with a TNFi (adjusted HR 3.2; 95% CI 1.4–7.5) [25].

At present, there is no specific recommendation for preventing PJP in patients treated with biologics. Administration of trimethoprim–sulfamethoxazole in patients at risk to develop PJP is effective, but due to the low incidence of PJP infection in this population this measure is not regularly employed.

Histoplasmosis

Histoplasmosis infection associated with the use of biologics appears to be more frequent than tuberculosis in the USA. Perhaps one of the main reasons is the presence of histoplasmosis-endemic areas in the USA as well as the low

Table 8.2 Opportunistic fungal infections in patients treated with biological drugs

Author	Type of study	N° of patients	Treatments	Time of follow up	Pathology	Incidence/risk/%
Fungal infections						
Pneumocystosis						
Baddley et al. 2014 [11]	Cohort	33,324 (16 with Pneumocystis)	TNFis cDMARDs	9 years (1998–2007)	ICDs	20% (16/80 non-viral OI)
Salmon-Ceron et al. 2011 [14]	Registry (RATIO)	45 with OI (5 with Pneumocystis)	TNFis	3 years	ICDs	11% (5/45 non-TBC OI)
Rutherford et al. 2018 [25]	Registry (BSRBR)	19,282 (15 with Pneumocystis)	Biologics	13 years (2002–2015)	RA	13% (15/114 non-TBC OI)
Takeuchi et al. 2008 [44]	Cohort	5000 (22 with Pneumocystis)	Infliximab	6 months	RA	0.4%
Koike et al. 2009 [45]	Cohort	7091 (16 with Pneumocystis)	Etanercept	6 months	RA	0.2%
Kaur et al. 2007 [46]	Review of case reports	84 cases	Infliximab	5 years (1998–2003)	RA CD	—
Bruce et al. 2016 [47]	Registry (BSRBR)	17 cases	TNFis cDMARDs	3 years	RA	IR: 2 cases /10,000 pt/year (TNFis) IR: 1.1 cases /10,000 pt/year (cDMARDs)
Histoplasmosis						
Lee et al. 2002 [48]	Case reports	10 cases	Infliximab Etanercept	1 year (2001)	RA CD	90% (9/10) (Infliximab) 10% (1/10) (Etanercept)
Wallis et al. 2004 [49]	Registry	639 granulomatosis infectious (42 with HT)	Infliximab Etanercept	4 years (1998–2002)	ICDs	6% (39/639) (Infliximab) 0.4% (3/639) (Etanercept)
Hage et al. 2010 [50]	Case reports	19	TNFis	—	ICDs	—
Olson et al. 2011 [51]	Case reports	26 (15 with TNFis)	TNFis cDMARDs	11 years (1998–2009)	RA	—
Vergidis et al. 2015 [52]	Review of case reports	98 cases	TNFis	11 years (2000–2011)	ICDs	—
Coccidioidomycosis						
Bergstrom et al. 2004 [53]	Cohort	985 (13 with CCD + TNFis and 4 with CCD + cDMARDs)	TNFis cDMARDs	5 years (1998–2003)	ICDs	RR: 5.23 (1.54–17.71) (TNFis vs cDMARDs)
Taroumian et al. 2012 [54]	Case reports	44	Biologics cDMARDs	2 years (2007–2009)	RDs	18% (8/44) (only with cDMARDs) 25% (11/44) (only with biologics) 57% (25/44) (with biologics + cDMARDs)

OI opportunistic infection, *TBC* tuberculosis, *HT* histoplasmosis, *CCD* coccidioidomycosis, *RA* rheumatoid arthritis, *CD* Crohn's disease, *ICDs* inflammatory chronic diseases, *RDs* rheumatic diseases, *TNFis* tumour necrosis factor inhibitors, *cDMARDs* conventional disease-modifying antirheumatic drugs, *IR* incidence rate, *RR* relative risk, *pt* patient

prevalence of tuberculosis in this country [40]. Incidence rates for histoplasmosis are higher in the Midwest, especially Indiana and Arkansas [60].

TNF-α is critical for controlling primary and secondary infection with *Histoplasma capsulatum* (HC) [61]. This could be the reason why fungal infection due to HC has been reported as an OI in patients treated with TNFi, especially infliximab [6].

In 2002, 10 cases of HC were reported in patients who had received infliximab (9) or etanercept (1) to treat RA or CD. All the patients lived in HC-endemic geographic regions of the USA. Nine patients were treated in the intensive care unit, and one patient died [48]. Data collected through the Adverse Event Reporting System of the US Food and Drug Administration for January 1998–September 2002 reported 39 cases for infliximab and 3 for etanercept with a rate/ratio

of 6.30; $p < 0.001$ [49]. A more recent report collected 19 cases in Indianapolis of HC infection between the year 2000 until early 2009. All were associated with TNFi administration (infliximab, etanercept, and adalimumab), which involved a broad spectrum of diseases, the most frequent being RA and CD. Most patients were also treated with immunosuppressive therapy. Lung involvement was present in 15 patients, and pulmonary symptoms were the prominent clinical feature in 13 patients; however, symptoms of progressive disseminated histoplasmosis were also present in 17 patients. No patient died [50]. Olson et al. [51] reviewed all patients with RA who developed histoplasmosis and were treated at the Mayo Clinic in Rochester, MN, USA, between January 1998 and January 2009. Twenty-six cases were found, of which 15 were in patients receiving a TNFi (infliximab, etanercept, and adalimumab). Two patients died due to unrelated causes of the infection. Again, the lung was the primary organ involved although a few patients also had systemic fungemia.

Symptoms of histoplasmosis are not specific, which requires a high index of suspicion for early diagnosis [50]. Difficulties arise if the patient lives in a nonendemic area of histoplasmosis; in that case, and if the suspicion of *Histoplasma* infection is high, a careful travel history, among other epidemiological and clinical situations, must be taken [50]. For patients who are candidates for TNFi therapy who live in an endemic area of histoplasmosis, several actions are necessary to perform before starting treatment to detect those who are at risk of developing the fungal infection. However, routine screening for antibodies and antigens to HC is not recommended because the results can be negative in patients who will become infected by HC after starting treatment with a TNFi [3, 50]. If infection occurs, aggressive antifungal therapy and withdrawal of the TNFi are required. Whether TNFi treatment can be resumed after the fungal infection has been treated is debatable, and some experts recommend that TNFi therapy should not be restarted [50, 52]. However, among the 19 cases noted above, TNFi was administered again in 7 patients after completing antifungal treatment for a mean duration of 10 months, and none had experienced a relapse during the follow-up of 1–8 years [50].

On the other hand, Olson et al. [51] restarted TNFi in 4 of 15 patients, and one of these patients had a recurrence. Another study reviewed 98 patients diagnosed with histoplasmosis [52] after therapy with TNFi. Again, infliximab was the most common biologic involved (67.3%). Concomitant corticosteroid use (OR 3.94; 95% CI 1.06–14.60) and higher urine *Histoplasma* antigen levels (OR 1.14; 95% CI 1.03–1.25) were found to be independent predictors of severe disease. In three patients with mild infection, the TNFi was maintained; the outcome of the process was favorable. However, as the authors emphasize, the standard of care is to withdraw the biologic. Treatment with TNFi was resumed in 25 patients after a median time of 12 months since the diagnosis of histoplasmosis. Throughout the 32 months of follow-up, three patients had a recurrence of the infection; two of these had restarted therapy with TNFi at 6 months after HC diagnosis, one of whom died. One relevant conclusion of this study was that resuming TNFi appears to be safe, providing that antifungal treatment has been administered for 12 months [52]. Nonetheless, if TNFi is restarted, patients would need close monitoring that includes clinical and/or laboratory evidence of the absence of recurrent disease [52].

There have been case reports of *immune reconstitution inflammatory syndrome* (IRIS) once treatment for histoplasmosis (or tuberculosis) was started [50, 52, 62]. IRIS is an exaggerated inflammatory reaction to a disease-causing microorganism that can occur when the immune system begins to recover following treatment of the infection. The diagnosis of this syndrome is frequently a challenge. In a patient with histoplasmosis, IRIS is suspected if negative serology accompanies clinical worsening to the fungal infection, and improvement occurs after steroid therapy [50].

Other Fungi

Coccidioides species causes coccidioidomycosis, which is an endemic infection in some areas of California, New Mexico, Texas, and Arizona as well as in parts of Mexico and some Central- and South-American countries. Most cases of coccidioidomycosis are asymptomatic (60%); however, coccidioidomycosis can also be present as pneumonia or as a disseminated infection [53]. In a study of this fungal infection, performed between May 1998 and February 2003, 13 cases were diagnosed after administering infliximab (12) and etanercept (1). Two patients died, and the rest had a complete resolution of the infection after treatment with fluconazole [53]. Interestingly, the local recommendations to prevent this fungal infection from these endemic areas include coccidioidal serologic tests for IgM and IgG; however, the review of these cases showed that TNFi-coccidioidomycosis infections are more likely to be acute and not detected by these screening measures [53]. In a more recent study [54] performed on patients with rheumatic and autoimmune diseases, 44 patients had a diagnosis of coccidioidomycosis; six patients had asymptomatic infection, diagnosis of which was established by a positive serologic test. The rest had pneumonia or disseminated infection. Eight patients received a biologic alone, 25 a combination of biologics and cDMARDs, and eight only cDMARDs. Among the biologics, one patient had been treated with abatacept and the rest with a TNFi (infliximab, etanercept, adalimumab). Biologics and/or cDMARD therapy was resumed in 33 patients with no dissemination or complications of coccidioidomycosis. The authors recommend antifungal therapy for 6–12 months and restarting biological treatment in those with active rheumatic disease and negative serology for fungal infection [54].

A few cases of disseminated aspergillosis have been also reported, especially, with infliximab in patients with IBD [63].

Virus (See Table 8.3)

Varicella-Zoster Virus

Varicella-zoster virus (VZV) induces varicella (or chickenpox) and HZ (or shingles). It was considered for many years a mild condition. However, the development of severe forms, even deadly, in immunocompromised patients, changed that perception. Furthermore, postherpetic neuralgia is a troubling sequela to HZ that occurs frequently. An estimated 15% of patients still report pain at 2 years after the flare. Factors favoring neuralgia are age (>80 years), the severity of the prodrome, and acute phase pain [77, 78]. Early treatment is desirable; however, it is not clear whether prompt intervention can prevent neuralgia [78–80].

In 2007, Smitten et al. [64] reported the risk of HZ in RA, reviewing two databases from the USA and UK. This retrospective study, conducted between 1998 and 2002, included 122,272 (USA) and 38,621 (UK) patients with RA. The adjusted HR of HZ for the patients with RA compared with the reference group of non-RA patients was 1.91 (95% CI 1.80–2.03) in the US database (including a subgroup treated with infliximab, etanercept, and anakinra) and 1.65 (95% CI 1.57–1.75) in the UK database (no biologics included). The risk of HZ in the US database was compared with a reference group of individuals with nonuse of DMARDs or oral corticosteroids on the index date. Almost all combinations, except bDMARDs plus cDMARDs (adjusted OR 1.38; 95% CI 0.83–2.27), showed a significantly increased risk for HZ; adjusted ORs: biologics only 1.54 (95% CI 1.04–2.29); cDMARDs only 1.37 (95% CI 1.18–1.59); oral corticosteroids only 2.51 (95% CI 2.05–3.06); biologics plus oral corticosteroids 2.44 (95% CI 1.26–4.73). Importantly, for both

Table 8.3 Opportunistic viral infections in patients treated with biological drugs

Author	Type of study	N° of patients	Treatments	Time of follow up	Pathology	Incidence/risk/%
Viral infections						
Varicella-zoster virus						
Rutherford et al. 2018 [25]	Registry (BSRBR)	19,282	Biologics	13 years (2002–2015)	RA	47% (54/114 non-TBC OI)
Smitten et al. 2007 [64]	Case control	1,660,893 (19,120 with HZ)	Biologics cDMARDs	12 years (1990–2002)	RA	OR: 1.54 (1.04–2.29) (Biologics) OR: 1.27 (1.10–1.48) (cDMARDs)
Strangfeld et al. 2009 [65]	Registry (RABBIT)	5,040 (82 with HZ)	TNFis	5 years (2001–2006)	RA	IR: 11.1 cases/1000 pt/year
McDonald et al. 2009 [66]	Cohort	20,357 (713 with HZ)	TNFis cDMARDs	7 years (1998–2005)	RA	HR: 0.62 (0.40–0.95) (Etanercept) HR: 0.53 (0.31–0.91) (Adalimumab) HR: 1.32 (0.85–2.03) (Infliximab)
Serac et al. 2012 [67]	Registry (RATIO)	24 with HZ	TNFis	3 years (2004–2007)	RA	OR: 1 (Etanercept) OR: 3.25 (0.93–11.36) (Adalimumab) OR: 3.94 (0.93–16.65) (Infliximab)
Long et al. 2013 [68]	Case control	108,604 (2677 with HZ)	TNFis Thiopurines Corticosteroids	≥6 months	IBD	OR: 1.81 (1.48–2.21) (TNFis) OR: 1.85 (1.61–2.13) (Thiopurines) OR: 3.29 (2.33–4.65) (TNFi + thiopurines) OR: 1.73 (1.51–1.99) (Corticosteroids)
Veetil et al. 2013 [69]	Cohort	813 (84 with HZ)	Biologics cDMARDs Corticosteroids	27 years (1980–2007)	RA	OR: 1.24 (0.56–2.74) (Biologics)
Galloway et al. 2013 [70]	Registry (BSRBR)	15,554 (320 with HZ)	Biologics cDMARDs	6 months	RA	IR: 1.6 cases/100 pt/year (Biologics) IR: 0.8 cases/100 pt/year (cDMARDs)

Table 8.3 (continued)

Author	Type of study	N° of patients	Treatments	Time of follow up	Pathology	Incidence/risk/%
Curtis et al. 2016 [71]	Cohort	69,726 (2215 with HZ)	Biologics Tofacitinib	4 years (2010–2014)	RA	IR: 3.87 cases/100 pt/year (Tofacitinib) IR: 1.95 cases/100 pt/year (Adalimumab) IR: 2.55 cases/100 pt/year (Certolizumab) IR: 2.08 cases/100 pt/year (Etanercept) IR: 2.12 cases/100 pt/year (Golimumab) IR: 2.71 cases/100 pt/year (Infliximab) IR: 2.67 cases /100 pt/year (Rituximab) IR: 2.48 cases/100 pt/year (Tocilizumab) IR: 2.33 cases/100 pt/year (Abatacept)
Yun et al. 2016 [72]	Cohort	29,129 biologic indications (423 episodes of HZ)	Biologics	5 years (2006–2011)	RA	IR: 1.97 cases/100 pt/year (All biologic cohort)
García-Doval et al. 2010 [73]	Cohort	4,655 (from BIOBADASER) 114,279,124 pt/year (from CMBD) (3830 with HZ in total)	TNFis	3 years (2003–2006)	ICDs	IR: 32 cases/100,000 pt/year (hospitalization)
Cytomegalovirus						
Domm et al. 2008 [74]	Review of case reports	5	Infliximab	0–2 years	ICDs	—
Progressive multifocal leukoencephalopathy						
Molloy et al. 2017 [75]	Review of case reports	8	Biologics	—	ICDs	—
Hepatitis B virus						
Koutsianas et al. 2017 [76]	Review of case reports	—	Biologics	—	ICDs	29–64% (HBs-Ag + with TNFis) 1.7% (past HBV infection with TNFis) 30–60% (HBs-Ag + with Rituximab) 1.7% (past HBV infection with Rituximab) 1–10% (HBs-Ag + with Abatacept) <1% (past HBV infection with Abatacept)

HZ herpes zoster, *HBV* hepatitis B virus, *HBs-Ag* HBs-antigen, *RA* rheumatoid arthritis, *IBD* inflammatory bowel disease, *ICDs* inflammatory chronic diseases, *TNFis* tumour necrosis factor inhibitors, *cDMARDs* conventional disease-modifying antirheumatic drugs, *IR* incidence rate, *HR* hazard ratio, *RR* relative risk, *pt* patient

data sources, steroids were associated with an increase of HZ independent of the associated medication [64].

A preliminary study from the German register RABBIT reviewed 82 patients with RA and HZ. Thirty-nine of these patients were treated with monoclonal TNFi, 23 patients with etanercept, and 24 patients with cDMARDs. The adjusted HR for age, RA severity, and steroid use demonstrated an increased risk of HZ in patients treated with a monoclonal TNFi (infliximab and adalimumab) (HR 1.82; 95% CI 1.05–3.15); however, that significance was lower than the predefined HR threshold of 2.5. No significance was found when HZ in patients with etanercept was compared

with controls: HR 1.36 (95% CI 0.73–2.55) [65]. To add more confusion to this topic, in a study published in the same year conducted on veterans with RA, both etanercept and adalimumab were associated with a lower risk for HZ [66].

The French prospective registry RATIO, designed to collect the opportunistic infections in France from 1 February 2004 to 31 January 2007, validated 24 cases of HZ, most of them in RA. The risk of HZ with a monoclonal TNFi (infliximab or adalimumab) compared with the soluble receptor etanercept was significantly higher (OR 3.49; 95% CI 1.12–10.90; $p = 0.0316$). The multivariate analysis of 24 HZ cases and 96 controls showed a timing-risk dependency, decreasing the risk of HZ as long as the TNFi is maintained [67].

To evaluate the risk of HZ in patients with IBD, a retrospective study and nested case-control was performed. Patients with CD, ulcerative colitis, and undefined IBD were included. As a whole, and after adjustment, the patients with IBD had an increased risk of HZ compared with the non-IBD patients (HR 1.49; 95% CI 1.42–1.57). In the nested case control, a multivariate-adjusted analysis showed a risk of increase with TNFis (OR 1.81; 95% CI 1.48–2.21). Steroids and thiopurines also had an independent increase of risk for HZ [68]. On the other hand, a study conducted in Minnesota aimed to determine the incidence of HZ in patients with RA was compared with a similar resident cohort without RA; the only factors associated with HZ were erosive disease and treatment with hydroxychloroquine or steroids. However, neither methotrexate nor biologics were associated with HZ [69].

A publication based on data from the BSRBR in patients with RA focused on the risk of shingles in 11,881 patients treated with TNFis (infliximab, adalimumab, or etanercept) or without TNFis (3673 patients). The shingles incidence was 1.6 (95% CI 1.4–1.8) and 0.8 (95% CI 0.6–1.1) per 100 patient years for TNFis and non-TNFis, respectively. When the risk of both populations was compared, the patients treated with TNFis had an increased risk of developing shingles (HR 1.7; 95% CI 1.1–2.7) versus the non-TNFi-treated patients. Finally, the risk of each TNFi was analyzed, showing that the lower risk occurred in patients treated with adalimumab, followed by etanercept, and finally infliximab (adjusted HR 1.5, 95% CI 0.9–2.4; HR 1.7, 95% CI 1.0–2.7; and HR 2.2, 95% CI 1.4–3.4, respectively) [70]. A more recent publication of the British database included 19,282 patients with 106,347 years of follow-up treated with biologics (a TNFi [etanercept, adalimumab, infliximab, certolizumab], rituximab, or tocilizumab). The overall incidence for nontuberculous opportunistic infections was 134 cases per 100,000 patients per year. HZ was the most common nontuberculous OI observed in the register with an incidence of 59 cases per 100,000 patients per year. No difference in the rate of serious HZ by drug class was found [25].

A recent retrospective study in RA [81] analyzed the Medicare data from 2006 to 2011 and included patients treated with TNFis, tocilizumab, rituximab, or abatacept. None of the biologics showed an increased risk of HZ after being analyzed individually; nonetheless, steroids again led to a greater risk of developing HZ compared with the referent population, and the risk doubled depending on the dose, i.e., adjusted HR for prednisone <7.5 mg 1.55 (95% CI 1.25–1.93) and 2.35 (95% CI 1.81–3.04) for patients taking prednisone over 7.5 mg. Another interesting finding of this study was the low number of patients vaccinated against HZ (range from 0.4% in 2007 to 4.1% in 2011) (75). Tofacitinib is a Janus kinase inhibitor approved to treat RA. Adverse events are comparable with that of biologics except for HZ. There is a suspicion from clinical trials that the HZ infection rate appears to be higher with tofacitinib than with biologics [82]. In a real-world study using data from Medicare, the risk for HZ was approximately double with tofacitinib than with biologics (TNFi, ABA, tocilizumab, and rituximab) [71].

A point of discussion has been whether vaccination for HZ in patients with RA or other rheumatic/autoimmune disorder is recommended. A recent study, that included patients with RA and other autoimmune disorders, suggested that due to the high risk for HZ, patients as young as 40 years could benefit from HZ vaccine [72]. The 2015 American College of Rheumatology (ACR) Guideline for the Treatment of Rheumatoid Arthritis conditionally recommends that in patients with RA over age 50, the HZ vaccine should be administered before the patient receives biologic therapy or tofacitinib for their RA [38]. On the other hand, the European League Against Rheumatism (EULAR) has not adopted an official position on this topic. After analyzing the data from BIOBADASER and a national database in 2010, a group of Spanish researchers found that patients with rheumatic diseases exposed to TNFis had a 10-fold increase in the rate of hospitalization due to VZV infections. However, the absolute rate of hospitalizations due to chickenpox and shingles in exposed patients was low (approximately 3 cases per 10,000 person-years of exposure for shingles and chickenpox). That result leads the authors to conclude that the benefits of vaccination probably do not outweigh the risks related to the prevention of severe or hospitalized HZ infection [73]. An editorial in the journal disagreed with the main conclusion of the previous report, and although the authors admit that the rates of hospitalized and complicated HZ were low, they conveyed that the benefits of the HZ vaccine went beyond preventing hospitalization [83]. A randomized, double-blind, placebo-controlled trial with a live attenuated Oka/Merck VZV vaccine included 38,546 adults over age 60. The results demonstrated a reduction of the burden of illness due to HZ by 61.1% ($p < 0.001$), a reduction of the incidence of postherpetic neuralgia by 66.5% ($p < 0.001$), and finally the incidence of HZ was reduced to 51.3% ($p < 0.001$) [84] A new adjuvanted HZ subunit vaccine was studied in a randomized-placebo phase III in people ≥50 years old. The overall efficacy against HZ was 97.2% and no difference in efficacy or safety

between the stratified age groups (50–59, 60–69 and ≥70 years) was found [85].***

In summary, although steroids are undeniably related to an increased risk of developing HZ, the results with the various biologics have been dissimilar or at least conflicting. On the other hand, although the HZ vaccine is recommended in the USA for patients with RA before administering biologics, in other parts of the world, such as Europe, it is currently not a standard of care.

Cytomegalovirus

The frequency of seropositivity to cytomegalovirus is high in the healthy population; it ranges from 87% to 100% for cytomegalovirus-IgG [86]. Until 2008, a few cases of systemic, retinal, or hepatic involvement had been reported after treatment with TNFi, all with infliximab. Most patients had IBD, only one case had RA, and another had Behcet's disease [74]. As occurs in many other situations in which the number of cases is very small, it is difficult to establish whether biologics are decisive in developing these complications, especially when all patients are receiving concomitant treatment with immunosuppressive agents and/or steroids.

Progressive Multifocal Leukoencephalopathy

JCV is the causal agent of progressive multifocal leukoencephalopathy (PML), which is a very severe and rare condition that involves the central nervous system of immunocompromised patients. As stated in the review of Molloy et al. [75], immunosuppressive therapies to treat rheumatic conditions were classified as either "Class 2, low risk of PML" (rituximab, belimumab, cyclophosphamide, azathioprine, mycophenolate, methotrexate) or "Class 3, very low risk of PML" (TNFi, tocilizumab, abatacept, ustekinumab, anakinra, tofacitinib). In biologics, the main concern has been related to the use of rituximab. In total, 26 cases of PML have been diagnosed to date in patients receiving rituximab for rheumatic diseases. Nonetheless, confounders were present in many cases [3, 75]. Fortunately, this infection, many times fatal, is a rare event, given it appears in less than 1 in every 20,000 patients with RA treated with rituximab [3, 75]. On the other hand, the role of rituximab in the development of PML remains unknown.

Hepatitis B Virus

Patients with hepatitis C do not appear to have a problem receiving biologics. In fact, TNFis are relatively safe for these patients [3]. However, the situation is completely different in patients with hepatitis B virus (HBV) infection. Any patient intending to receive biologics must be screened for HBV serologic status [3]. The test should include, at least, B serum antigen (HbsAg), which is a marker of acute or chronic infection; surface antibody (HbsAb), usually linked to previous vaccination; and core antibody (HbcAb), which when positive in isolation, might indicate an occult infection. In case a hidden infection is suspected, excluding B virus replication (HBV DNA) is recommended [3, 87, 88].

In a retrospective study performed in Taiwan on patients with RA under TNFi treatment, the authors reported that none of the 10 patients with positive HBsAg and HBV DNA had a reactivation of HBV when they received prophylactic treatment with lamivudine. However, five of eight (63%) patients who were positive for both HBsAg and HBV DNA who had not received antiviral treatment developed an HBV reactivation. The infection was under control within 3 months after starting antiviral therapy [88].

A similar situation occurs when patients are treated with biologics other than TNFis. Reactivation of HBV infection has been reported in patients treated with rituximab, abatacept, tocilizumab, and ustekinumab [76].

In summary, there is no formal contraindication to treatment with biologics in patients with chronic HBV infection. For these patients, antiviral treatment, the specifics of which would depend on national guidelines, must be administered. Close contact with the hepatologist or an expert in hepatitis B is advisable [76].

Acknowledgments FEDER, ISCIII, and the research project PI16/000474.

Conflicts of Interest **EMM**: None.

ChPR: Received speaking fees or funding for research projects from Pfizer, Lilly, Novartis, and Roche.

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Part II

Viral Arthritides

The Pathophysiology of Arthritis Due to Viruses and Vaccines

9

Andreas M. Reimold

Abbreviations

ACPA	anticitrullinated protein antibody
APL	antiphospholipid
ASIA syndrome	Autoimmune/inflammatory syndrome induced by adjuvants
CCP	cyclic citrullinated protein
CMV	cytomegalovirus
EBV	Epstein-Barr virus
ENA	extractable nuclear antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HTLV-1	human T cell leukemia virus-1
IFN	interferon
ISG	interferon-stimulated genes
MHC	major histocompatibility complex
sAg	surface antigen
β2GP1	beta-2 glycoprotein-1

Viruses Causing Arthralgias or Arthritis

At least 219 viral species are known to infect humans and increasingly sensitive methods in describing the human virome will likely describe orders of magnitude higher numbers of viruses that colonize and possibly infect humans [1]. A viral infection is an extremely common cause of joint symptoms, especially arthralgias (Table 9.1). Viruses generally affect all age groups. The main routes of infection are airborne, person-to-person, and occasionally via fomites. Once in the body, viruses spread widely during viremia but can also be distributed to specific sites through immune complexes or by trafficking within specific cell types.

Susceptibility to arthritis is influenced by host factors: age, genetics (susceptibility to outsize inflammatory or autoimmune reactions), gender, presence of comorbidities, and health status of joint tissues [2, 3]. In addition, viral factors also influence the likelihood of joint involvement: virulence of the virus, ability to produce toxins, degradability of viral products, and tissue tropism to joints.

Host factors affecting risk of bacterial septic arthritis are more numerous than those recognized for viral arthritides. For example, local factors predisposing to bacterial infection such as direct joint trauma, joint surgery or open reduction of fractures, arthroscopy, intraarticular injection, and prosthetic joint implants are not prominent in the pathogenesis of viral arthritis. However, host factors that affect a robust immune response are relevant to both bacterial and viral infections: extremes of age, use of biologics and immunosuppressant drugs, and comorbidities such as renal failure, malignancy, and diabetes mellitus. Finally, social factors are important for susceptibility to viral infection in terms of overall health such as low socioeconomic status or chronic alcohol abuse, or for specific exposures such as risky sexual behavior or intravenous drug abuse [4].

Mechanisms of Viral Infections

Innate Immune Responses

Multiple mechanisms must be considered to explain the joint features of viruses. Acute viral infection has systemic effects without direct invasion of the joints in most cases. Release of cytokines such as IL-1 and IL-6 is part of the febrile response that includes arthralgias. The first line of defense is the innate immune system [5].

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_9

Table 9.1 Viruses that cause articular symptoms

	Arthralgia/arthritis	Maximum duration	Synovial invasion
Parvovirus B19	60% of adults	Months, and rare recurrences	
Rubella virus and rubella vaccine	30% of women	2 weeks, rarely up to a year	Yes, also immune complexes
Alphaviruses (e.g., Chikungunya)	Arthralgia/arthritis in 100%, chronic arthritis in Chikungunya	Mostly 3–6 months, rarely >3 years	Virus persists in synovial macrophages
Ebola virus	Arthralgia common, synovitis 14%	63% after 9 months	Likely
Ebola vaccine rVSV-ZEBOV	Arthritis/arthralgia in 22%	Usual 18 days, occasionally months	Yes [124]
Flaviviruses:			
Dengue	Arthralgia 80%		
Zika	Arthralgia common, no arthritis	Usually 7 days	
Mumps	Arthritis is rare	Few weeks	
Enteroviruses: (Coxsackievirus, Echovirus)	Arthritis is rare	Most days to weeks, rarely up to months	Echovirus occasionally isolated from joints
Adenovirus	Arthritis is rare	Self-limited	
Herpes viruses:			
Varicella-zoster virus	Arthritis is rare	Self-limited	Occasionally isolated from joint Virus is latent in B cells
Epstein–Barr virus	Rare, large joint arthritis	Self-limited	
Herpes simplex virus	Rare, arthritis during generalized HSV-1 infection	Self-limited in <3 months	
Cytomegalovirus	Rare, arthritis in the immunosuppressed	Months	
Hepatitis A	Arthritis is rare	Usually self-limited, rarely chronic, relapsing with associated vasculitis	
Hepatitis B	Arthritis in up to 25%	Self-limited, never chronic arthritis	Immune complex formation
Hepatitis C	Arthralgias common Arthritis in up to 20%	Long-term oligoarthritis or RA-like arthritis	Immune complex formation with mixed essential cryoglobulinemia
Hepatitis E	Arthralgia		Cryoglobulinemia [125]
HIV	Painful articular syndrome, rare progression to arthritis	24 hours	
	Reactive arthritis	Chronic, relapsing	
	Psoriatic arthritis	Chronic	
	Diffuse infiltrative lymphocytosis syndrome (DILS)	Chronic sicca symptoms	
	Immune reconstitution inflammatory syndrome	May include RA-like symptoms	
HTLV-1	Chronic medium- and large joint arthritis [126]		

Data from Moore TL and Syed R. Specific viruses that cause arthritis. UpToDate 08-07-2018

1. *Pattern recognition receptors* (*PRRs*): PRRs such as retinoic acid inducible gene 1 (RIG-1), melanoma differentiation-associated gene 5 (MDA-5), and toll-like receptors (TLR-s) are expressed by leukocytes, epithelial cells, fibroblasts, and brain cells to initiate signaling pathways that converge at the activation of transcription factors (interferon [IFN]-regulatory factor 3 and IRF 7, NF-κB) to upregulate type I IFNs.
2. *Type I interferons*: Interferons binding to receptor (IFNAR) then lead to expression of multiple IFN-stimulated genes (ISGs), proinflammatory cytokines, and chemokines. ISGs include oligoadenylate synthetase (OAS), ribonuclease L (RNaseL), IFN-inducible dsRNA-dependent protein kinase (PKR), and myxovirus resistance (Mx) protein that are all involved in antiviral effects on different aspects of a virus' life cycle. ISGs are additionally simulated by other innate pathways (double-stranded RNA, single-stranded RNA) and feedback loops related to IFN signal signaling proteins.
3. *Apoptotic pathways*: Apoptotic pathways are also upregulated by innate immune system activation. The intrinsic apoptosis pathway is initiated by the release of cytochrome C from mitochondria and results in a cascade leading to the effector caspase-3. The extrinsic apoptotic pathway is mobilized by TNFα, TRAIL or FASL and leads to the death pathway involving FADD and Caspase 8. Some viruses produce antiapoptotic proteins such as IAP and Bcl2, and CHIKV hides in apoptotic blebs,

which are taken up my macrophages without an inflammatory response.

After viral infection, there is a rapid induction of type I interferon (IFNα and IFNβ) and the production of proinflammatory cytokines by resident cells. An acute viral infection that is contained and then eliminated by the host is a common pattern of infection. Examples are rhinovirus and influenza virus, which as a rule do not result in chronic or latent infections.

Adaptive Immune Responses

Up to 90% of viral pentapeptides are shared by the human proteome, making it likely that these sequences usually do not elicit an immune response due to tolerogenic mechanisms. However, in the setting of impaired tolerance or a break in tolerance produced by a vaccine adjuvant, exposure to these viruses makes the possibility of autoimmunity more likely [6, 7].

The adaptive immune system has an important role in the pathogenesis of joint symptoms and is a key part of the body's response to all arthritogenic viruses. The humoral immune response first produces IgM antibodies in the acute phase, then undergoes class switching to IgG antibodies, which, when neutralizing, can help to clear the virus and prevent reinfection in many cases. IgG responses can occur within days of the first IgM responses, can be neutralizing, and therefore can be markers of a robust and successful humoral immune response. Persistence of an IgM response has correlated with persistent Chikungunya virus (CHIKV) infection and prominent joint symptoms while later recurrence of an IgM response can signal reinfection or reactivation of the virus [8].

The cellular immune response to viruses consists of a rapid mobilization of CD4+ and CD8+ T cells. CD4+ responses can skew toward Th1 and produce cytokines such as TNFα, IL-1b, IFN-γ, and IL-12 while Th2 and Th17 responses produce cytokines such as IL-4, IL-13, and IL-17. The activation of CD8+ T cells is the classic immune response of cytotoxic cells that attack infected cells presenting viral antigens in conjunction with MHC Class I on their surface. Rapid clonal expansion of antigen-specific T cells and the acquisition of effector functions (providing T cell help or generating T cytotoxic capability) occur after viral infection and lead to rapid clearing of the virus in most cases. After the initial immune phase, the T cells have a contraction phase where most responding cells are eliminated while a small number of memory T cells survive long term and are available to respond to future reinfections. One example is the rapid CD8+ T cell responses to CHIKV, which has been associated with production of IL-4, IL-10, and IFN-γ [9].

Latent and Chronic Viral Infections

Latent infection can be defined clinically as viral infection without viral replication, but without viral eradication. After an acute primary infection, the period of viral latency may be punctuated by clinical or subclinical relapses. A latent, occult, noninfectious form of the virus can be due to an integrated genome or as episomal nucleic acid. Immunologic mechanisms of viral latency may include: (1) evasion of a cell-mediated immune response, e.g., by down-regulation of MHC class I molecules so that T cell (CTL and NK) recognition is lost; humoral antibodies may cap viral antigens on the cell and cause them to shed (e.g. measles/SSPE), leaving the host cell surface without viral proteins and (2) infection of immunoprivileged sites such as the brain.

Episomal latency refers to viruses maintaining their nucleic acid separately from that of the host cell, usually in the cytoplasm. Advantages of episomal latency are that the cytoplasmic virus may not enter the nucleus, avoiding the nuclear bodies called nuclear domain 10 (ND10) that restrict viral gene expression [10]. Disadvantages to episomal latency include increased exposure to cellular defenses and degrading enzymes. Examples of viruses using this strategy are HSV-1, HSV-2, and VZV in sensory ganglia and brain; CMV in lymphocytes, macrophages, and myeloid progenitor cells; and EBV in B lymphocytes [11].

In proviral latency, the viruses' genome is integrated into the host's DNA. Advantages for the virus include that host cell division leads to viral replication and that removing the virus without killing the host cell is not possible using current technology. Disadvantages are that the virus needs to enter the cell's nucleus, requiring packaging proteins that allow for this step. HIV is an example for proviral latency [12].

A persistent or chronic viral infection refers to a continuously replicating virus that remains infectious but that may or may not cause ongoing clinical symptoms. With a chronic persistent (replicative) infection, the essential functions of the host cell may be largely intact (e.g., DNA and RNA synthesis, protein synthesis). Examples include HIV infection, most cases of hepatitis C virus infection, and certain adult cases of hepatitis B infection [13].

Viruses that demonstrate latent infection also have the potential for lytic replication (Table 9.2). One example is parvovirus B19 that persists in blood and bone marrow of immunocompromised patients (chemotherapy, HIV, congenital immunodeficiencies, transplants) and is commonly harbored in human skin, making it difficult to ascribe causality for skin lesions by PCR rather than clinical means [12, 14]. Parvovirus B19 maintains latency by regulating inflammatory pathways that include AP-1, SP1, NF-κB pathway, TNFα, and p53 through virus-encoded NS1 protein [15]. Two mechanisms have been proposed for viral reactivation of herpesviruses (e.g., HHV6, HHV7, EBV, CMV) and par-

Table 9.2 Potentially arthritogenic viruses showing lytic as well as latent infection

	Clinical conditions
Herpesviridae	
HSV-1	Cold sores, encephalitis, pharyngitis, keratitis, whitlow
HSV-2	Genital herpes
VZV	Chicken pox, shingles
EBV	Mononucleosis, lymphoma (Burkitt's, NHL), nasopharyngeal ca
CMV	Congenital effects, mononucleosis
Parvoviridae	
Parvovirus B19	Fifth disease, gloves-and-socks syndrome Children: large joint oligoarthritis; adults: RA-like pattern of arthritis
Others	
HIV	HIV-associated arthritis Painful articular syndrome Reactive arthritis, psoriatic arthritis, USpA Rheumatoid arthritis Immune reconstitution inflammatory syndrome
Hepatitis B	Hepatitis, RA-like joint pattern of arthritis
Hepatitis C	Hepatitis, RA-like pattern of arthritis Vasculitis, sicca syndrome, arthralgias/arthritis, and fibromyalgia Cryoglobulinemia: large joint nonerosive oligoarthritis (e.g., at ankles)
HTLV-1	Chronic large and medium joint oligoarthritis. Associated eye, skin, muscle disorders

Data from Traylen et al. [127]

voviruses: (1) a stimulus elicits a potent immune response with a cytokine storm, resulting in viral reactivation; and (2) a stimulus may cause relative immunosuppression (hypogammaglobulinemia, reduced B cell count, and activation of monocytes and T cells) that leads to viral reactivation [16]. The exact virus-encoded proteins involved in triggering viral reactivation are not well understood in many cases. Speculation about the mechanisms has included major gene rearrangements as well as alteration of nucleotide sequences in transcription machinery binding sites, leading to a switch from latent to lytic infection [17].

The listing of acute, latent, and persistent viral infections does not always correlate well with observed clinical patterns. For example, parvovirus B19 is clinically an acute infection without chronicity in immunocompetent hosts, yet viral sequences may remain detectable by molecular techniques in the bone marrow. Nonreplicating parvovirus B19 DNA has been readily demonstrated in bone marrow of healthy controls as well as in 7 of 22 (32%) rheumatoid arthritis patients [18]. However, features of RA did not correlate with the presence of parvovirus B19. At the same time, persistence of parvovirus in the setting of additional mutations in the immune system can lead to further insights into immune functioning. One recent example was a chronic parvovirus infection in a patient with a novel mutation in the ELANE (neutrophil elastase) gene [19]. This patient had decreased neutrophil NET (neutrophil extracellular trap) formation and decreased IL-8 and IL-12 production resulting in decreased neutrophil chemotaxis and antiviral immunity. The patient experienced daily fevers, rash, and inflammatory arthritis with chronic parvovirus infection.

Mechanisms of Chronic Arthritogenic Viral Infection

Certain viruses can cause a chronic infection, some directly in joint structures and others elsewhere in the body. Examples include HIV, hepatitis B and C, EBV, and CHIKV. The initial host antiviral response results in elaboration of IL-10 and type I interferons, which provide immunosuppressive signals that are essential for viral persistence. On the other hand, gp130-dependent cytokines such as IL-6, IL-11, and IL-27 continuously support proinflammatory responses of the humoral and cellular immune systems. Common gamma-chain cytokines IL-2, IL-7, and IL-21 help to maintain the viability and function of the T cell pool and their levels can be modulated to optimize immune responses and achieve viral clearance. The complexity of the system is further reinforced by observations of diametrically opposite immune effects by certain cytokines in different circumstances. One example is the effects of type I interferon on the clearance of lymphocytic choriomeningitis virus (LCMV) virus in a mouse model, which enhances clearance for chronic strain Cl-13 while decreasing clearance for lymphocytic choriomeningitis virus–Armstrong (LCMV-ARM) strain [20].

In chronic viral infection, an ongoing potent immune response may not be desirable due to the potential for causing host damage from uncontrolled T cell expansion. On the other hand, a muted immune response reduces immune surveillance and permits viral persistence. During chronic viral infection, immune exhaustion can occur by which both CD4+ and CD8+ T cells lose their main effector functions [21]. Exhausted CD4+ cells lose most of their production of effector cytokines such as IL-2, TNFα, and IFN-γ, have increased expression of inhibitory cell-surface receptors such as PD-1 and CTLA4, and increased production of IL-10 and IL-21. Exhausted CD8+ T cells have increased expression of inhibitory receptors PD1, LAG-3, 2B4, Tim3, and CD160, with decreased cytokine elaboration, decreased proliferation, and decreased cytotoxic activity. Over time, the population of effector T cells dwindles and the antiviral response also decreases. Further research efforts are underway to manipulate cytokine levels in order to limit or reverse T cell exhaustion.

Chikungunya virus, an alphavirus, is a rare example of a virus causing recurrent arthralgias or even polyarthritis up to 3 years after initial infection [22]. Indeed, CHIKV has been demonstrated to set up a chronic infection with tropism for

synovial tissues such as synovial macrophages and osteoblasts [23]. Virus persists intracellularly, thus evading immunosurveillance and allowing viral persistence. At the same time, infection of macrophages/monocytes and other immune system cells leads to chemokine and cytokine production and inflammatory cell recruitment, all resulting in clinical swelling and pain at the joints.

Ebola, another alphavirus, is also known to cause chronic arthralgias and persistent arthritis, sometimes for years after initial infection. For Ebola, the most frequent symptom of survivors is asymmetric arthralgias. For example, in a group of 44 survivors reporting arthralgias with their initial infection, 63% had musculoskeletal pain 9 months after discharge, of which 14% had synovitis on examination [24].

Immune complex deposition is a further mechanism by which certain viruses cause joint symptoms. For example, hepatitis B virus can lead to immune complex formation followed by deposition in synovial tissue, and hepatitis C virus can result in immune complex deposition leading to mixed cryoglobulinemia [11].

Mechanisms That Allow Autoimmunity

A genetic component underlies all of autoimmunity. Most autoimmune arthritic diseases have been associated with genetic susceptibility loci, especially in the MHC class I and class II loci. As one common example, it has been found that the HLA-DRB1 loci are associated with at least 30 autoimmune conditions [25]. These genetic loci are associated with tailored and possibly an overactive immune response, so that individuals with these loci produce more autoantibodies even without the presence of overt disease. It has been proposed that breakdown of immune tolerance occurs especially in those individuals with aberrant presentation of antigen on MHC class II to autoreactive T cells. Such a mechanism of broad reactivity may persist over generations if it provides a survival advantage by allowing the clearance of an infectious organism that otherwise evades the immune system [26].

Molecular Mimicry

Autoreactivity through molecular mimicry is often the most important mechanism of autoimmunity in viral infections. In this scenario, self-proteins would bear stretches of identity or a high percentage of similarity to viral sequences. With the break in tolerance caused by the virus (or by a vaccine and its adjuvant), an immune response becomes possible against both the viral sequences and the similar or identical self-protein sequences. In one experiment, over 600 monoclonal antibodies were made against 11 viral proteins and tested for reactivity with 14 mouse organs [27]. The results showed that an antivirus monoclonal had crossreactivity against host tissues in 3.5% of cases, making molecular mimicry a common phenomenon in humoral immune responses.

In addition, molecular mimicry has been demonstrated in the T-cell responses of cellular immunity [28]. Homology was found between the protein sequence in the polymerase gene of hepatitis B virus and myelin basic protein (MBP), a key target in the animal model of multiple sclerosis, experimental autoimmune/allergic encephalomyelitis (EAE). Injection of the viral sequence into animals indeed caused T cell reactivity and an EAE-like disease [29]. In a separate work, in vitro studies of autoreactive T cell clones directed at MBP could be activated with viral peptides [30]. While the presentation of antigen to autoreactive T cells by APCs in conjunction with MHC class II and simultaneous crossreactivity with viral sequences are not uncommon phenomena, it has been proposed that not all such interactions lead to florid autoimmune disease. It is likely that only when the viral sequence mimics a particularly potent disease-inducing self-epitope does the full-blown autoimmune disease develop. In most other cases, the self-reactivity and crossreactivity do not progress to clinical symptoms [31]. Theories of molecular mimicry in the etiology of autoimmune and rheumatic diseases have been advanced in spondyloarthritis, antiphospholipid syndrome, rheumatoid arthritis, and systemic lupus, among others [32–35].

Bystander Activation

Bystander activation is a further mechanism causing an autoimmune response to virus infection or to vaccination [31]. Three pathways can be envisioned. First, a viral infection can lead to the activation of potent antigen-presenting cells such as dendritic cells. Both appropriate antigen presentation and the release of cytokines by APCs could activate self-reactive T cell clones and lead to autoimmune manifestations. Secondly, virus-specific CD8+ cytotoxic T cells will traffic to sites of virally infected cells where they will lyse the cells. The milieu of dying and infected cells will attract multiple inflammatory cells such as macrophages and T cells, causing release of cytokines such as TNFα and lymphotoxin [36]. This cytokine release can lead to bystander killing of uninfected cells. Thirdly, a similar mechanism of inflammatory cytokine release by CD4+ T cells has been proposed to result in further bystander killing [37].

Polyclonal Activation and Superantigens

HCV is an example of a virus that can act as a polyclonal activator on specific B and T lymphocyte populations [38]. Such polyclonal stimulation results in enhanced antigen pro-

cessing and the presentation of self-antigens, setting the stage for an autoimmune response. In addition, it was found that chronic HCV infection disrupts the tolerance mechanism that normally deletes autoreactive B cells, therefore increasing the risk of developing autoimmune antibodies. A related effect is seen with viral or virus-induced superantigens, which activate large numbers of polyclonal T cells that express particular Vb gene segments of which some could be specific for a self-antigen [39]. A massive cytokine release results. Of the viruses considered in this chapter, superantigens can be part of infection by CMV, EBV, and HIV.

Epitope Spreading

Epitope spreading refers to expansion of the immune response to target not just the initial epitope but also additional epitopes over time [40]. This mechanism was demonstrated in an animal model using Theiler's virus infection of the central nervous system and leading to recognition of host myelin epitopes [41]. Key factors in autoimmunity induction were a virus that induced Th1 immunity, the host's genetic background, and chronic viral infection.

Cytokines and Chemokines

Chemokines signal inflammatory cell trafficking into sites of inflammation while cytokines are key effectors of pro- and antiinflammatory responses. Cytokine effects include shaping of the T helper cell pathways such as Th1, Th2, and Th17. Viruses causing arthritis may cause local damage by high-level cytokine release in the host at times through transactivation of the host cytokine gene by viral products. One example is the transactivation of the proinflammatory IL-6 promoter by the NS1 protein of parvovirus B19, leading to high IL-6 cytokine levels and making it a key component of the host's inflammatory response to infection [42]. The complex relationship between viruses and cytokine levels is further highlighted by the actions of human papillomavirus, which inhibit the actions of proinflammatory JAK/STAT transcription factors and yet activate STAT-5 with downstream activation of the ATM and ATR DNA damage response pathways, resulting in HPB genome amplification [43].

Viruses as Protection Against Autoimmunity

There is a flip side to the commonly discussed induction of autoimmunity by viral infections, namely a protective effect of certain viral infections against the development of autoimmunity. Some examples include the decreased rate of type 1 diabetes in those with Group B Coxsackievirus, EBV infection, or LCMV infection [44]. Several mechanisms have been proposed [31]: (1) inducing apoptosis of autoreactive cells, (2) influencing cellular trafficking of autoreactive cells away from target organs, or (3) immune suppression and production of antiinflammatory cytokines (IL-10, TGFβ).

One line of inquiry has raised the possibility that HBV infection protects against the development of SLE. Studies in Colombian and Chinese populations with relatively high rates of endemic HBV demonstrated that hepatitis B infection occurred at lower rates in their SLE patients than in the general population [45, 46]. In Colombians, 2.5% of 117 SLE patients versus 10.7% of healthy controls had anti-HBc antibodies while in the Chinese cohort, 2.33% of SLE patients versus 9.57% of the general population had HBsAg. Any potential mechanism for protection against autoimmune disease by HBV infection awaits further investigation.

Overall, a definite causative or protective effect for viruses in autoimmune disease has been difficult to demonstrate. Humans have multiple chronic or remote viral infections, and most have been cleared at the time of autoimmune disease onset. The genetic background and environmental exposures are additional factors influencing autoimmunity.

Common Rheumatologic Syndromes Associated with Viral Infections

Sjögren's Syndrome

Sialotropism is a feature of several viruses and has led to an association with Sjögren's syndrome. For example, hepatitis C virus and HIV are both recognized as causing sialadenitis, sicca symptoms, and distinctive autoantibody production. Because of these associations, the classification criteria for primary Sjögren's syndrome require that HCV and HIV are ruled out as etiologies. Previous studies have also detected Epstein–Barr Virus (EBV), Coxsackie virus, and human T-lymphotropic virus (HTLV-1) in salivary gland tissue of Sjögren's patients without providing conclusive evidence of causality for the syndrome [47–51]. Besides infection of CD4+ T cells, HTLV-1 was shown to infect salivary gland epithelial cells and result in the upregulation of molecules involved in cell adhesion, inflammation, and migration [52]. In addition, a recent report added hepatitis delta virus detection in half of the samples tested from 15 primary Sjögren's syndrome patients [53]. In a mouse model, expression of hepatitis D virus antigens in salivary tissue recapitulated the pathologic features of Sjögren's syndrome including autoantibody formation, reduced salivary flow, and the formation of lymphocytic foci. Previous animal studies using in vivo expression of proteins from hepatitis C virus or HTLV-1 recapitulated incomplete Sjögren's features, most notably lacking induction of SSA or SSB [54, 55]. Therefore, it may

be that only specific viruses are associated with the full range of Sjögren's syndrome while others lack specificity.

Vasculitis: Giant Cell Arteritis

Herpes zoster has been investigated as a cause or trigger of giant cell arteritis based on both histopathologic and epidemiologic studies [56]. Varicella-zoster virus induces a T cell–mediated immune response, causes vascular changes such as multinucleated giant cell formation and gradient of involvement strongest at the adventitia and weakest at the intima (similar to GCA), and has been detected by some but not all investigators using molecular techniques in temporal artery biopsies [57, 58]. In epidemiologic studies, a retrospective review of administrative data in over 16 million adults, age over 50 years, and no previous GCA was able to identify almost 6000 cases of GCA [59]. An antecedent herpes zoster infection was documented in 3.1–6.0% of cases in the two datasets used. In a multivariate analysis, the increased risk of complicated herpes zoster followed by GCA had a hazard ratio of 1.99 (95% CI 1.32–3.02) and 2.16 (95% CI 1.46–3.18) in the two datasets. This roughly twofold increase in risk of GCA after a specific viral infection is clearly only one of the possible triggers of GCA.

Human papilloma virus DNA has been identified in 16 of 22 temporal artery biopsy samples, but other studies seeking *Chlamydia pneumoniae*, parvovirus B19, and herpesviruses in biopsy samples showed no difference between GCA patients and controls [60]. In addition, a recent microbiome study on GCA biopsy samples showed no increases in individual microorganisms [61].

Vasculitis: Polyarteritis Nodosa

Polyarteritis nodosa (PAN) related to viral infection has been recognized as having a separate pathogenesis from classic PAN. The best-studied is hepatitis B infection, but hepatitis C virus, HIV, human T cell leukemia virus-1, cytomegalovirus, EBV, and parvovirus B19 are additional associated agents [62]. The association of HBV with PAN is relatively common, with 10–54% of PAN cases in various series proven to have HBV, although the incidence has been decreasing in areas of higher HBV immunization [56, 63]. The vasculitis often occurs in the first 6 months of infection when both viral replication and the host's antibody formation are most active. This results in two proposed pathogenic mechanisms for the vasculitis: (1) toxicity to the vessel wall by direct invasion of virus and (2) IgG-containing immune complex and complement deposition at the endothelium with damage resulting from the immune response [62]. Nevertheless, demonstration of hepatitis B viral antigen in vessel walls has rarely been successful, making immune complex deposition the more common mechanism of vasculitis [64]. By contrast, classic PAN is associated with activation of both innate and adaptive immune pathways but without the prominent immune complex deposition [65].

Vasculitis: Cryoglobulinemic Vasculitis

Rheumatologists are often consulted on mixed cryoglobulinemia related to hepatitis C infection. Now in the era of direct-acting antiviral therapy for hepatitis C, the cryoglobulinemia and cryoglobulinemic vasculitis greatly improve or resolve after achieving a sustained virologic response. However, persistent cryoglobulinemia has been described in up to 20% of patients up to 2 years after viral cure [66]. In addition, patients with cryoglobulinemic vasculitis and cirrhosis may have delayed clearance of virus and remain at risk of vasculitis relapse despite HCV eradication. In all such cases cryoglobulins were present before antiviral treatment, so that HCV-related cryoglobulinemia is not known to begin de novo after successful HCV clearance [67].

Besides HCV, cryoglobulinemic vasculitis is occasionally identified in association with other viral infections. A French nationwide survey and additional literature review identified 45 patients with non-HCV cryoglobulinemic vasculitis with eight patients having a viral association, including four with HBV and one each having CMV, EBV, parvovirus B19, and HIV [68].

Evaluating for Viral Infection Versus Rheumatoid Arthritis

Most transient arthralgias related to an acute viral infection resolve without specific treatment in 6 weeks. Even when joint symptoms persist past this 6-week mark, a viral infection is not a common diagnosis made by rheumatologists. In a study of 322 patients presenting with less than 1 year of polyarthralgias or inflammatory arthritis, only 2 (0.6%) were diagnosed with a viral etiology (one HCV and one parvovirus B19) [69]. In a Finnish study of 60 patients with acute reactive arthritis, parvovirus B19 was found in only 3% of subjects [70].

Rheumatoid arthritis (RA) is in the differential diagnosis for viral infections that give persistent symptoms for more than 6 weeks regardless of viral clearance. The clinician commonly considers hepatitis C or HIV and uncommonly includes CHIKV, Ebola virus, and HTLV-1 (Table 9.1) [71]. The travel history as well as sexual and drug use history will be informative for gauging the initial likelihood of these viral infections. The clinical presentation of viral arthritis can be very similar to RA, with a small joint polyarthritis, elevation

of inflammatory markers (but viral infection sometimes leaves acute phase proteins and complement remarkably unchanged), and even positivity for RF and aCCP in 5–10% of CHIKV cases [8]. However, the marginal erosions of RA are generally not part of the presentation in viral arthritis.

The inflammatory syndrome seen in viral arthritis and rheumatoid arthritis can have similar pathophysiologic mechanisms. For example, alphaviruses such as Ross River virus and CHIKV can cause macrophage recruitment to joints, prominent intraarticular secretion of inflammatory cytokines and chemokines, with further recruitment of inflammatory infiltrates, all resulting in an amplification loop of inflammation [72]. The pathogenesis includes upregulation of the transcription factor NF-κB and production of the cytokines TNFα, IFN-γ, and MCP-1, all contributing to a proinflammatory environment.

Determination of anticitrullinated peptide antibody (ACPA) status has become a valuable diagnostic tool in assessing for rheumatoid arthritis in the setting of viral infection [73]. For the diagnosis of rheumatoid arthritis, anti-CCP antibodies have a specificity of 94% and a sensitivity of 70% [74]. Nevertheless, ACPAs from RA patients can also demonstrate cross-reactivity as shown in a BLAST search using the essential epitopes recognized by ACPAs. The amino acid sequences recognized by ACPAs were also found in 56 viral, 1,383 fungal, and 547 bacterial proteins and were recognized in vitro by ACPAs in the cases tested [75]. Anti-CCP antibodies are found in up to 33% of patients with HCV-related arthralgia/arthritis, a subgroup representing about 4% of all hepatitis C patients [76]. Patients with HCV infection but no joint symptoms rarely show aCCP positivity. By comparison, RF can be found in 50–80% of patients' HCV-related arthralgia/arthritis and in 9.7% of HCV patients without joint symptoms [77]. Titers are usually low to intermediate in viral infections compared to the highest levels seen in inflammatory arthritis. Therefore, there will be a small group of true rheumatoid arthritis patients among the HCV+ population, and these can be recognized more easily if they show the somewhat RA-specific features of high anti-CCP titers, erosive disease, and rheumatoid nodules [78]. The detection of multiple autoantibodies in HCV+ patients additionally includes ANA, SSA and SSB, anti-DNA, p-ANCA and c-ANCA, and anticardiolipin, demonstrating the wide immunoreactivity induced by viral infection [78].

Persistence of alphavirus particles or viral antigens in joint tissues is linked to chronic joint symptoms due to the six so-called "arthritogenic alphaviruses": Chikungunya virus (CHIKV), Barmah Forest virus (BFV), Mayaro virus (MAYV), Ross River virus (RRV), o'nyong-nyong virus (ONNV), and Sindbis virus (SINV) [5]. Alphaviruses are known to persist in tissue sanctuaries where they may evade immune clearance long term. For CHIKV, one report in humans demonstrated viral antigens in macrophages and viral RNA in synovial tissue 18 months after initial viral infection [79]. These findings have not been confirmed by subsequent studies, but ongoing IgM serologic responses have been shown to persist up to 6 months [80]. The result may be ongoing virus production, long-term IgM antiviral responses in the host, and more chronic clinical illnesses that may include a true arthritis. Reactivation of virus also becomes a concern whether due to immune suppression (chemotherapy, organ transplant, arthritis treatment) or other senescence and weakening of the immune system [81].

EBV is a further chronic viral infection that may show mechanisms related to RA development. EBV resides lifelong as a latent infection in the resting B cells of most individuals. Citrullinated proteins derived from EBV nuclear antigen (EBNA) can give rise to ACPA responses years before the onset of clinical rheumatoid arthritis. In addition, they cross-react with citrullinated fibrin and, therefore, show further features of ACPA responses relevant to RA pathogenesis [82].

Increased Viral Infection in Patients on Tofacitinib

While the risk of bacterial, fungal, and mycobacterial infections has received extensive attention with use of biologics in rheumatic diseases, the risk of viral infections is much less well studied. Recently, the mechanisms by which tofacitinib reduces antiviral responses have been examined in detail, focusing on in vitro plasmacytoid dendritic cells (PDC) and their production of interferon alfa (IFN-α) [83]. In an in vitro culture model using human cells, the authors found that tofacitinib induces PDC apoptosis by inhibiting expression of the antiapoptotic molecules, BCL-A1 and BCL-XL. In addition, tofacitinib strongly inhibited the production of IFN-α by toll like receptor (TLR)-stimulated PDCs. Also, tofacitinib suppressed the IFN-α-induced upregulation of TLR3 on synovial fibroblasts, thus inhibiting their cytokine and protease production in response to TLR3 ligation. Tofacitinib also counteracted the reduction of viral replication that otherwise results from the presence of IFN-α. Overall, tofacitinib leads to decreased production of IFN-α, decreased downstream cytokine and protease production from IFN-α, and permits increased viral replication. These mechanisms may help to explain the increased viral infection rates seen in patients on tofacitinib.

Vaccination and Autoimmunity

The same mechanisms that were discussed above for viruses to cause autoimmunity are relevant to viral vaccines and autoimmunity: genetic susceptibility, environmental factors,

a break in tolerance, molecular mimicry of the vaccine's viral protein compared to host antigens, and downstream activating mechanisms such as cytokine effects, bystander activation, polyclonal activation, and epitope spreading. The adjuvant used in a vaccine is an important participant in the impairment of immune tolerance. Most vaccines would not elicit an immune response without an adjuvant, indicating that the human immune system is inherently tolerant of many different pathogenic proteins and nucleic acids. Once immune tolerance to the pathogens is broken by the adjuvant, a neutralizing immune response becomes feasible.

Antiphospholipid Antibodies: Viruses and Vaccinations

Formation of antiphospholipid antibodies has been described after infection with hepatitis B virus, hepatitis C virus, HIV, varicella-zoster virus, rubella, CMV, and parvovirus B19 [84]. There has subsequently been interest in evaluating the induction of APL antibodies by vaccines.

The presence of chronic HBV infection triggers the formation of antiphospholipid antibodies. In one study of 50 HBV patients, anticardiolipin IgG was seen in 12.6%, β2GPI in 2.1%, and lupus anticoagulant in 1.4% of subjects. A meta-analysis has confirmed the elevated risk of aCL and β2GPI development in HBV patients [85, 86]. A recent study reported the risks of APL antibody formation in healthy controls versus virus-infected individuals. The findings showed increased relative risks of elevated anticardiolipin levels in virally infected patients: HIV with RR 10.5 (95% CI 5.6–19.4), HCV with RR 6.3 (95% CI 3.9–10.1), hepatitis B virus RR 4.2, (95% CI 1.8–9.5), and Epstein-Barr virus RR 10.9 (95% CI 5.4–22.2) [87]. These risks were clinically important as thromboembolic events were increased in patients with elevated aPL antibodies who had HCV (9.1%, 95% CI 3.0–18.1) and those with HBV (5.9%, 95% CI 2.0–11.9). HIV has separately been shown to lead to arterial and venous thrombotic events and HIV vasculopathy [88].

In studies of susceptibility to antiphospholipid syndrome after hepatitis B vaccination, a group of 85 healthy students was immunized [89]. One month later, 8 of 85 (9.4%) showed an increased titer of IgG anti-β2GP1. A potential mechanism was the binding of recombinant hepatitis B sAg to the fifth domain of the β2GP1 antibody, leading to induction of antibody production. No thromboembolic event occurred in this short-term study. A clinical trial of HBV immunization of lupus patients also showed no increase in lupus flares following immunization [90].

Influenza immunization was shown to elicit new formation of anticardiolipin but not β2GP1 antibodies but at the same rates in SLE patients (12 of 101 cases) as in healthy control (7 of 101), p = not significant [91]. Three meta-analyses showed no consistent adverse impacts of influenza immunization on SLE patients [92].

Starting almost 60 years ago, polio, smallpox, and mumps vaccinations were reported to elicit a transient rise in RF production in healthy individuals, but without clinical sequelae [93]. More recently, influenza vaccine has been shown to elicit a large number of autoantibodies (RF, ANA, ENA, ANCA, APL and others) in healthy subjects as well as autoimmunity patients but a transient increase in titers and lack of long-term autoimmunity are the rule [94]. Exceptions are coming to attention at the case report level and will require future follow-up [95].

Mechanisms of Vaccine Adjuvant Action

A reaction against a vaccination can come from the viral sequences used or from the adjuvant [96]. Adjuvants are essential since immunization with viral protein or nucleic acid alone would not elicit a protective immune response. The main adjuvants used in human vaccines are alum (aluminum salts), oil in water emulsions (MF59, AS03), and AS04 (theTLR4 ligand monophosphoryl lipid A absorbed to alum) [97]. Adjuvant activity has also been postulated to reside in bacteria, oils, drugs, silicone, and other environmental agents [98]. Multiple mechanisms of action have been investigated for adjuvants, starting with activation of innate immune mechanisms and downstream coupling to adaptive immunity. Aluminum stimulates dendritic cells to enhance antigen presentation, stimulates TLRs, promotes eosinophil activation, serves to attract neutrophils, and enhances production of chemokines and cytokines [99]. Evidence has been presented that alum might signal through the pattern recognition receptors (PRR) of the innate immune system and downstream activate the NLRP3 inflammasome and caspase1 [100]. The inflammation-induced local accumulation of uric acid may represent a damage-associated molecular pattern (DAMP) and act as an endogenous adjuvant capable of recruiting dendritic cells and activating T cells at sites of immunization [101]. The cytotoxicity induced by alum additionally releases host DNA, which is a further DAMP [102]. In an effort to improve the specificity of adjuvant targeting, newer adjuvants are under development as agonists for specific toll-like receptors, including TLR3, TLR4, TLR5, TLR7/8, and TLR9 [97].

Arthritis and Vaccinations

When live viruses are used as strains for vaccination, their growth and survival properties may result in articular manifestations in some instances. Rubella virus vaccine and an Ebola vaccine candidate serve as examples.

Rubella Virus and Rubella Vaccine

Rubella virus causes joint symptoms in up to 60% of those infected with worse symptoms in women [103]. Joint symptoms typically resolve within a few weeks yet an occasional patient will have episodic or chronic arthropathy that lasts months to years [104]. Multiple mechanisms have been invoked to explain long-term joint findings after rubella infection. Age, female gender, and MHC type all contribute to susceptibility. Rubella virus has been isolated in synovial fluid for up to a month following initial infection. The virus can be isolated from PBMCs of symptomatic individuals up to 6 years after infection and thus could be trafficked into joints. In vitro, rubella virus can be grown in primary human synovial tissues and in chondrocyte-derived cell lines, providing a mechanism for viral replication within the joint itself. The initial rubella virus infection may not be cleared despite a high-level antibody response by the humoral immune system. This raises the possibility of immune complex formation and deposition within the joints. Thus, there are both intra- and extraarticular reservoirs of rubella virus that can contribute to chronic symptoms.

The rubella vaccine is a live, attenuated virus that has a reduced capacity to replicate in synovial tissues and chondrocytes compared to wild-type virus. Rubella vaccination causes a similar range but decreased severity of joint symptoms compared to natural rubella infection, with arthralgias in 25% of recipients and frank arthritis in 1% [105]. At the extreme, rubella vaccination has been reported to be associated with a chronic arthritis lasting at least 1 year [106]. The virus has been detected in vaccinated women with a chronic arthropathy by using RT-PCR on PBMCs [107]. Although the incidence of chronic arthritis in rubella-vaccinated individuals is very low, specific HLA-DRB1 (DR2 and DR5) haplotypes may represent a genetic risk factor for chronic joint symptoms [108]. Despite some similarities in presentation, rubella vaccination is not a known cause of rheumatoid arthritis [107, 109].

Ebola Vaccine

The search for an Ebola virus vaccine has allowed controlled experiments that provide insight into requirements for arthritic manifestations after viral infection [110]. A candidate Ebola vaccine (rVSV-ZEBOV) was produced by adding Ebola surface glycoprotein (ZEBOV) to a vesicular stomatitis virus (VSV). Three observations shed light on Ebola's arthritogenic effects. First, the vaccination virus rVSV-ZEBOV showed a tropism for synovial tissue, even though wild-type VSV alone does not. Second, expression of the viral ZEBOV protein was not sufficient. Instead, viral replication may be needed to cause arthritis. A replication-deficient vector encoding ZEBOV (Chimp adenovirus type 3-ZEBOV) did not cause arthritis despite expression of ZEBOV. Third, the development of arthritis after virus exposure requires a competent host immune system. For multiple viruses, development of arthralgias and arthritis may actually occur at a time of convalescence, once the adaptive immune response is already robust and has partly or fully cleared the virus. A similar situation applies to vaccine viruses, which may cause arthralgias and arthritis at 2 weeks post vaccination, even at a time when any live vaccine virus is cleared and the host response to the vaccine's viral determinants is well established. Of course, exceptions such as rubella do exist with prolonged persistence of viral particles being associated with a more chronic arthritis.

Hepatitis B Vaccine

Recently, a hypothesis was put forward that nonresponders to hepatitis B vaccine might be at risk for developing autoimmune disease [111]. The theory rests on the observation that HBV nonresponders have higher Th1 cytokine responses such as IL-18 and IFN-γ. These same cytokines are also implicated in the onset of multiple autoimmune conditions including rheumatoid arthritis, systemic lupus, type 1 diabetes, and celiac disease. Further evidence is needed to substantiate this hypothesis.

Vaccines and Autoimmunity: ASIA Syndrome

A focus on adjuvants has resulted in the definition of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome in 2011 [112]. The hypothesis is that adjuvants activate the innate immune system and cause multiple downstream inflammatory and even autoimmune effects. An adjuvant might mimic evolutionarily conserved molecules such as bacterial cell wall, lipopolysaccharide, or unmethylated CpG DNA, allowing binding to Toll-like receptors. In turn, this could cause activation of dendritic cells and macrophages, initiating chemokine and cytokine release locally and from downstream T cells and mast cells. In those with defective regulatory circuits or other genetic susceptibility, immune tolerance could be broken by this nonspecific activation of the immune system, leading to expansion of autoreactive lymphocytes and potentially the onset or unmasking of an autoimmune disease. Subsequently, the syndrome has been broadened to include a variety of exposures, including chronic exposure to silicone, tetramethylpentadecane, pristane, as well as multiple adjuvants [113].

Clinically, ASIA syndrome is described as typical or atypical features of autoimmune diseases occurring in genetically susceptible individuals after vaccination [114–116]. It is char-

acterized as having myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment, and memory loss. Four groups of individuals who might be susceptible to development of vaccination-induced ASIA syndrome have been proposed [117]:

1. Individuals with prior postvaccination autoimmune phenomena
2. Individuals with a medical history of autoimmunity
3. Individuals with a history of allergic reactions
4. Individuals with risk factors for autoimmunity (positive family history of autoimmune diseases, asymptomatic carriers of autoantibodies, certain genetic profiles).

Criteria requiring validation have been proposed for the ASIA syndrome [112]. The four major criteria were (1) an exposure to infection, adjuvant, or other stimuli before clinical manifestations, (2) clinical findings in muscle, joints (arthralgia, arthritis), chronic fatigue, neurologic findings, cognitive impairment, pyrexia, and dry mouth, (3) improvement once the inciting agent is removed, and (4) typical biopsy of involved organs. The four minor criteria are (1) antibodies directed at the adjuvant, (2) other clinical manifestations such as IBS, (3) specific HLA associations as in rheumatoid arthritis, and (4) development of an autoimmune disease.

Examples of ASIA Syndrome: HBV and HPV Vaccination

The association of autoimmune findings with previous immunizations remains a controversial topic. However, there are at least four examples of reliably vaccine-associated autoimmune reactions: Guillain–Barré syndrome after the 1976 swine influenza vaccine, immune thrombocytopenic purpura after measles/mumps/rubella vaccine, myopericarditis after smallpox vaccination, and narcolepsy with cataplexy after previous pandemic H1N1 influenza virus vaccination [93, 118].

Hepatitis B vaccine consists of recombinant hepatitis B surface antigen with aluminum hydroxide as the adjuvant. The immune or autoimmune reactions after hepatitis B vaccination have been presented by multiple groups. In studies of susceptibility to antiphospholipid syndrome after hepatitis B vaccination, a group of 85 healthy students was immunized [89]. 1 month later, 8 of 85 (9.4%) showed an increased titer of IgG anti-β2GP1. A potential mechanism was the binding of recombinant hepatitis B sAg to the fifth domain of the β2GP1 antibody, leading to induction of antibody production. A cohort of 93 patients who had the new onset of possible immune features after hepatitis B vaccination was examined by Zafir et al. [119]. The cohort was 70% female and all were seeking legal advice for their conditions. Twenty one percent had a personal or family history of autoimmunity. Onset of symptoms occurred a mean of 43.2 days after the last vaccination injection. A large spectrum of clinical involvement was found, including neurologic symptoms, systemic symptoms (fatigue, fever, weakness), musculoskeletal symptoms, and gastrointestinal symptoms. A new disease was diagnosed in a substantial proportion of the series: neurologic disease in 25.8% (e.g., multiple sclerosis, CIDP, Guillain–Barré), central pain syndrome (20.5%), SLE in 9.6%, and RA in 8.6%. The criteria proposed by the authors for ASIA syndrome were met in 80 of 93 (86%) patients.

Human papilloma virus vaccine also utilizes aluminum as an adjuvant. The occurrence of new and exacerbation of existing autoimmune phenomena have been reported after vaccination [120]. In an epidemiologic study based on the vaccine adverse event reporting systems, 2,207 possible cases of ASIA syndrome were identified for a rate of 3.6 cases per 100,000 doses of vaccine [121]. Common manifestations were fever (58%), myalgia (27%), and arthralgia/arthritis (19%). Reported severe findings were generally nonrheumatologic, such as postural orthostatic tachycardia, primary ovarian failure, immune thrombocytopenic purpura, acute cerebral ataxia, thyroiditis, and autoimmune hepatitis [122].

At the same time, the existence of ASIA syndrome has been disputed by some [90]. Ameratunga et al. pointed out that the category of environmental triggers and autoimmune phenomena leading to ASIA syndrome has expanded over time to now include macrophagic myofasciitis syndrome, the Gulf War syndrome, the sick building syndrome, silicone exposure, and the chronic fatigue syndrome. The authors focus on the aluminum-containing adjuvants in hepatitis B and human papilloma virus vaccines, which have been proposed as etiologic factors in some cases of ASIA syndrome. The authors further discuss that immunotherapy can use up to 500 times the amount of aluminum during a 3- to 5-year course of treatment but with no known association with ASIA syndrome. In addition, immunotherapy patients actually had a lower, not higher, rate of autoimmunity in a large pharmacoepidemiologic study. It is clear that large groups of vaccine recipients receiving a variety of vaccines and adjuvants will need to be studied to provide more clarity. Furthermore, current research is focusing on more targeted activation of the innate immune system by newer adjuvants with a goal of preventing nonspecific and autoimmune responses.

The National Vaccine Injury Compensation Program

Side effects from vaccine administration have long been recognized and ongoing litigation has led to the formation of the

National Vaccine Injury Compensation Program [123]. This mechanism has specified for potential compensation after certain vaccine side effects, with each having a time frame of occurrence after vaccination published in an "injury table." Multiple viral vaccines are on this list and potential side effects are specified for measles/mumps/rubella vaccine, rubella only vaccine, polio vaccines, and hepatitis B antigen–containing vaccine. Multiple other viral vaccines are listed without specifying individual side effects: varicella, rotavirus, hepatitis A, influenza, and human papilloma virus. Of these, the only specific mention of rheumatologic effects is a chronic arthritis that can occur 7 to 42 days after administration of rubella vaccine.

Three means have been established to qualify for compensation under the National Vaccine Injury Compensation Program [123]. (1) One must show that a specified injury found on the injury table occurred in the prescribed time interval. For example, this would be chronic arthritis starting 7–42 days after rubella vaccination. Meeting these criteria allows a legal "presumption of causation." However, multiple vaccines such as influenza and human papilloma virus have no specified injury and time course listed. (2) One must prove that the vaccine caused the condition, or (3) one must prove that the vaccine aggravated a preexisting condition. Therefore, if the injury from the vaccine is not on the injury table or no table injuries are listed for a particular vaccine, the petitioner must prove causation, which can be a difficult task. Also, in addition to meeting one of the three compensation qualifications, one must demonstrate that the injury lasted at least 6 months after the vaccination, resulted in a hospital stay or surgery, or resulted in death. No compensation is awarded if the court determines that there is greater evidence of a nonvaccine cause.

Conclusions

Viral infections frequently result in transient arthralgias but occasionally result in a long-lasting, even chronic, arthritis. With viruses such as rubella, mumps, and measles largely controlled through widespread immunizations, arthritic symptoms are increasingly recognized with emerging viruses such as CHIKV. Multiple factors control the growth of viruses and the host's response: viral properties, host characteristics including age and comorbidities, genetics, innate immunity, and adaptive immunity. Some viruses have characteristic target tissues that can include the joints, the salivary glands, and cells of the immune system. Autoimmune phenomena due to the presence of viral protein or nucleic acids are possible through immune responses such as molecular mimicry or by the production of autoantibodies. The adjuvants used in vaccines greatly augment host immune responses and at times lead to autoimmunity. The ASIA syndrome has been proposed as a set of clinical criteria to better classify the long-term symptoms reported by vaccine recipients.

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Hepatitis Arthritis: HBV and HCV

10

Rodolfo Perez-Alamino

Introduction

Hepatitis B virus (HBV), a dsDNA virus of the *Hepadnaviridae* family, is estimated to affect around 400 million people worldwide. Transmitted vertically, sexually, or through blood-borne contact (transfusion or intravenous drug use), around 95% of adults exposed to the virus will mount an appropriate immune response leading to eventual viral clearance [1]. With the introduction of efficient preventive measures, such as universal vaccination of infants, prevention of perinatal transmission, and vaccination of high-risk adults, several studies have shown a decrease in the incidence of acute HBV infection [2]. The geographic distribution of HBV infection can be described as follows: 88% of the global population lives in areas of intermediate ($HBsAg^+$ prevalence 2–7%) or high endemicity (>7%) corresponding to African and East Asian territories, where most infections occur from vertical transmission, whereas the remaining 12% lives in low endemicity areas ($HBsAg^+$ prevalence <2%), roughly corresponding to North Europe and the United States, where HBV infection usually occurs in adulthood. In western countries the incidence of HBV infection has been furtherly diminished by widespread vaccination programs since the 1980s [3, 4].

Hepatitis C virus (HCV) is a hepatotropic virus estimated to infect about 130–170 million people worldwide. Infection with the virus is known to result in severe morbidity and mortality, especially by liver complications (cirrhosis and hepatocellular carcinoma) in a significant number of patients after several decades of infection. As such, HCV represents a global health challenge with an estimated liver-related mortality of 350,000 people/year. It has been shown as one of the hepatic viruses most often associated with extrahepatic manifestations (EHMs), which present in up to two-thirds of infected patients [5].

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Extrahepatic syndromes may represent the first signal of HCV infection in some patients [6]. Some of the EHMs, including mixed cryoglobulinemia and non-Hodgkin B-cell lymphoma, have a significant prevalence with unequivocal data supporting a causal relationship. Other manifestations have been noted to have a high prevalence, including adverse cardiovascular events (stroke, coronary artery disease), kidney disease, metabolic diseases, and neuropsychiatric (depression, impaired quality of life) disorders [7]. With the introduction of effective direct-acting antivirals (DAAs), the opportunity to achieve HCV eradication has important implications from both a therapeutic and preventative perspective.

This chapter will outline the most important rheumatic manifestations associated with HBV and HCV infection, with a focus on arthritis, for which good evidence is available to support a linkage between infections and the clinical syndrome.

Diagnosis and Classification of Hepatitis B Virus Infection

The diagnosis of HBV infection relies mainly on serology (hepatitis B surface antigen [HBsAg], hepatitis B envelope antigen [HBeAg], anti-HBs, anti-HBc [hepatitis B core antibody], and anti-HBe antibodies) and serum HBV DNA levels [3]. Serologic tests are used for the differentiation between acute, chronic, and past (resolved) infection, whereas HBV DNA levels are required for distinguishing active chronic hepatitis from the inactive carrier state in chronically infected patients as well as for the detection of occult infection in resolved HBV infection [8] (Table 10.1):

1. *Acute hepatitis B* is characterized by high aminotransferases (alanine aminotransferase [ALT] >10 the upper limit of normal [ULN]) and positive HBsAg and IgM anti-HBc antibodies. These patients are rarely encountered in rheumatology practice.

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_10

Table 10.1 Laboratory in hepatitis B virus infection

		Chronic hep	Chronic hep		
	Acute hepatitis	HBeAg (+)	HBeAg (−)	Inactive carrier	Past infection
HBsAg	+	+	+	+	−
Anti-HBc	+	+	+	+	+
Anti-HBs	−	−	−	−	+/−
HBeAg	+	+	−	−	−
Anti-HBe	−	−	+	+/−	+
ALT	ULN (+++)	ULN	ULN	Normal	Normal
HBV-DNA	>20,000 IU/mL	>20,000 IU/mL	>2000 IU/mL	Undetectable	Undetectable

Abbreviation: ALT alanine aminotransferase, *ULN* upper limit normal
Adapted from Ref. [8]

2. *Chronic HBV infection* definition requires the presence of HBsAg in the serum for greater than 6 months. Most of the patients (70–80%) are inactive HBV carrier (normal ALT levels, low or undetectable serum HBV DNA) who rarely develop cirrhosis or its complications, whereas spontaneous clearance of HBsAg gradually occurs (1% per year). Approximately 20–30% of chronically infected patients though have active chronic hepatitis B (defined by elevated ALT and HBV-DNA levels) and, if left untreated, progress to cirrhosis and hepatocellular carcinoma. Two major subsets of *chronic hepatitis B* are recognized: *HBeAg positive and negative* [9].
3. *Past or resolved HBV infection* is defined by negative HBsAg and positive anti-HBc antibodies in the serum (with or without anti-HBs antibodies). Approximately 5–50% of rheumatic patients worldwide demonstrate this serologic profile. Among these patients, a small subset (<5%) can have occult HBV infection defined by the presence of HBV-DNA in the liver and occasionally in low levels in the serum (<200 IU/mL) [10]. This group of patients is challenging because they can rarely develop HBV reactivation with immunosuppression.

Pathogenesis of HBV Infection

HBV infection causes acute and chronic necroinflammatory hepatitis. The pathogenesis of HBV infection is still unknown. Massive hepatic injury occurring during chronic HBV infection seems to be immune mediated and depends on HBV-specific cytotoxic T-cells [11]; moreover, efficient control of HBV infection requires the synergic actions of both innate and adaptive immunity. Innate immunity induces in HBV-infected cells the production of type I interferons and several proinflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-10, some of which are reported to suppress viral replication and/or to exert non-cytolytic viral clearance. The persistence of HBV infection may be associated with CD8+ T-cell loss of the ability to secrete enough TNF-α to kill infected hepatocytes (so-called "exhausted phenotype"). It has been shown that in TNF-α knockout mice and in etanercept-treated mice, HBV infection persists, with subsequent increase in HBV-specific CD8+ T-cells, serum and liver HBV-DNA, and antigen expression [12].

Cellular immunity is critical for the outcome of HBV infection: HBV-specific T-cells are involved in the control of viral infection, while non-specific NK cells infiltrate the liver leading to hepatocellular injury. In humans, IL-6 in combination with TGF-β and IL-1β drive naive CD4+ T-cell to differentiate into Th17 cells in a HBc-dependent fashion [13]. Th17 cells can produce multiple cytokines that trigger the recruitment and activation of neutrophils leading to massive tissue inflammation. Recent reports showed that in chronic hepatitis B infection (CHB), antigen non-specific Th17 response is increased and that the peripheral Th17 frequency is associated with the degree of liver damage [14].

Recent reports suggest that humoral immunity also plays an important role in the immune response to HBV. HBcAg is able to directly activate B-cells to produce specific antibodies in the absence of regulatory T-cells. However, immunosuppression and B-cell suppression are associated with viral reactivation. B-cells are thus involved in liver inflammation in HBV-infected patients, but whether they influence disease progression is still a matter of debate [15].

Clinical Manifestations

Arthritis in patients with HBV occurs in both the prodromal phase of acute infection and during chronic HBV infection. Arthritis can be the only presenting feature of acute HBV infection and in the prodromal phase of infection often resembles rheumatoid arthritis (RA), with a symmetrical polyarticular distribution involving proximal interphalangeal joints, ankles, and knees [16]. The presence of rash, fever, malaise, or myalgia may provide clues to the underlying diagnosis. Arthritis symptoms typically last days to months and often resolve with the onset of jaundice. Rheumatoid factor (RF) can be elevated in around 25% of cases, whereas

C3 and C4 are found to be low in around 40%, indicative of an immune-complex-mediated process [17].

Hepatitis C

Clinical Manifestations

Hepatitis C virus infection is one of the best mimes among all diseases. It can induce a number of signs and symptoms involving almost any organ of the body. Many rheumatic disorders must also be clearly distinguished from the HCV manifestations.

Arthralgia is reported in 6–20% of patients infected with HCV. It usually involves large joints, sometimes with effusion, bilateral, and with a symmetric pattern. Arthralgia most frequently involves fingers, knees, and back [18]. It is significantly more frequent in patients with cryoglobulinemia vasculitis (CryoVas) compared with those without vasculitis. As similar than HBV, the presentation may mimic RA, even the frequent positivity of RF in patients infected with HCV might lead to misdiagnosis.

Zuckerman et al. have suggested two different subsets of HCV-related arthritis [19]:

1. A *RA-like subset*, principally involving small joints, in which the RF is often present but the elevation of ESR is less frequent than in classic RA. Rheumatoid nodules have never been reported and classically are considered as a non-erosive disease. Prolonged morning stiffness is common.
2. A less common *mono-oligoarthritis* involving medium-sized and large joints, often showing an intermittent course. This form seems more strictly related to the presence of cryoglobulins in the serum.

Mono-oligoarthritis or symmetrical RA-like polyarthritis is induced by HCV; consequently, different forms of arthritis must be considered in the differential diagnosis. The first subset must be distinguished from spondyloarthritis. When the HCV-related arthritis course is intermittent, crystal-induced arthritis should also be considered in the differential diagnosis. True RA may be easily mistaken for HCV-related RA-like polyarthritis, particularly in the early stages of the disease when erosions and rheumatoid nodules are usually absent. Myalgia is less common, affecting about 2–5% of patients with HCV [20].

Cryoglobulinemia vasculitis (CryoVas) is a small vessel vasculitis involving the skin, joints, peripheral nerve system, and the kidneys. Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperatures and dissolve with rewarming. During the last 15 years, progress has been made after the discovery of the HCV, which represents the cause of CryoVas in roughly 80%, mostly associated with a type II immunoglobulin (Ig) M kappa mixed cryoglobulin. Main symptoms include asthenia, purpura, arthralgia, myalgia, peripheral neuropathy, and glomerulonephritis [21]. Clinically or on imaging, there is no evidence of joint damage.

Skin is the most frequently involved target organ and is the direct consequence of the small-size vessel vasculitis. The main sign is *palpable purpura*, but chronic cutaneous ulcers may occur. Raynaud's phenomenon and acrocyanosis, which may evolve to digital ulcerations, can also occur. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex. The most frequently described form is a distal sensory or sensory-motor polyneuropathy. Polyneuropathy usually presents with painful, asymmetric paresthesia, which later becomes symmetric. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits. It represents 70–80% of cryoglobulinemia renal diseases and it is strongly associated with the type II IgM k mixed cryoglobulinemia. The most frequent presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency.

In a large cohort of patients with HCV-CryoVas, baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR], 5.31), central nervous system involvement (HR, 2.74), kidney involvement (HR, 1.91), and heart involvement (HR, 4.2) [22].

Apart from the detection of serum cryoglobulin, other laboratory abnormalities may provide surrogate evidence of the presence of cryoglobulinemia, such as low C4 serum complement fraction, decreased total hemolytic complement levels, presence of a serum monoclonal immunoglobulin or RF activity. Rheumatoid factor (RF) activity is found in 70–80% of patients with CryoVas, not correlated with the occurrence of joint disease. Anti-cyclic citrullinated peptide (anti-CCP) antibodies are usually absent in patients with HCV. Hypocomplementemia is a sensitive and important finding in CryoVas, being found in 70–90% of mixed cryoglobulinemia patients [23].

There are multiple immunologic factors predisposing patients infected with HCV to develop a CryoVas or other systemic rheumatologic manifestations. Chronic stimulation of B cells by HCV directly modulates B-cell and T-cell function and results in polyclonal activation and expansion of B cell–producing IgM with RF activity. There is an expansion of clonal CD21-/lowIgM1CD271 marginal zone-like B cells and a decrease of regulatory T cells [24]. Other factors are related to the infection by HCV of peripheral blood mononuclear cells, including peripheral dendritic cells, monocytes, and macrophages [25]. Under this trigger effect, oligoclonal or monoclonal IgM, which shares rheumatoid activity, is produced by a permanent clone of B cells that favors the appearance of immune complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM.

Fatigue and Fibromyalgia

In a large prospective study, 19% of 1614 patients infected with HCV fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia, and myalgia). Fatigue, with or without fibromyalgia, was the most frequent extrahepatic manifestation (35–67%) [26]. Many underlying factors were independently associated with fatigue, such as older age, female gender, presence of arthralgia/myalgia, as well as neuropsychological factors. Of note, after IFN-based treatment, only the group of patients with a sustained virologic response (SVR) showed a beneficial impact on fatigue. A benefit of treatment on arthralgia/myalgia was found in about 50% of patients, independently of the virologic response.

Sicca Syndrome

Sicca symptoms of either the mouth or eyes have been reported in 10–30% of patients infected with HCV. Less than 5% of patients with a defined Sjogren syndrome (SS) are HCV positive [27]. In a recent literature review, Younossi and colleagues reported a sicca syndrome prevalence of 11.9% in patients with HCV, with a risk ratio for sicca syndrome of 2.29 in patients infected with HCV compared with uninfected patients [28].

However, the criteria for SS diagnosis were based on the clinical questionnaire in some studies and were not well detailed. Although sicca symptoms are very common in patients infected with HCV, a characterized SS defined by the presence of anti-SSA or anti-SSB antibodies and typical salivary gland histology is uncommon. A large cohort study of patients with a definite SS (1993 international criteria) compared patients with HCV infection with those with a primary form. Patients with HCV-associated SS were older, more frequently male, and more frequently presented vasculitis, peripheral neuropathy, and neoplasia. They also had a different biological pattern: more frequently had a positive RF test, cryoglobulinemia, and less frequently anti-SSA or SSB antibodies [29]. The detection of HCV RNA and HCV core antigen in epithelial cells of patients with HCV-associated SS and the development of SS-like exocrinopathy in transgenic mice carrying the HCV envelope genes support the possibility of a direct impact of HCV on the development of sialadenitis [30].

Treatment

There is little experience in treating patients having HBV and HCV-associated arthritis, and the optimal treatment has not been established. The main objectives of treatment are to control the inflammatory process and, when required, to obtain a sustained clearance of the virus. Nonsteroidal anti-inflammatory drugs (NSAIDs), low doses of oral corticosteroids, and hydroxychloroquine (HCQ) are usually effective in controlling joint symptoms. Also, the risk for HBV and HCV reactivation during immunosuppressive therapy in patients with autoimmune diseases is a major concern.

Hepatitis B

Antiviral therapy is recommended for CHB patients who have HBV DNA levels >2000 IU/mL, serum aminotransferases above the upper limit of normal (ULN), and moderate to severe active liver necroinflammation and/or at least moderate fibrosis. The main objective of antiviral therapies are long-term suppression of viral replication, sustained HBeAg seroconversion for HBeAg+ individuals, and HBsAg clearance [31].

Long-term viral suppression is achieved in >95% cases with oral nucleic acid analogues (NAs), although HBsAg loss remains a hard to achieve target (<10%). Actually, therapies recommended for the treatment of CHB include *interferon-α (IFN)*, *pegylated-INF-α2a (PEG-IFN)*, and six *NAs* that can be classified into nucleoside (*lamivudine*, *telbivudine*, *emtricitabine*, *entecavir*) and nucleotide (*adefovir and tenofovir*) analogues, which have been shown a better safety profile [32]. Entecavir and tenofovir are potent HBV inhibitors currently recommended as first-line monotherapies. These agents have to be given either indefinitely (HBeAg-CHB) or for 12 months following HBeAg seroconversion in HBeAg+ CHB [33].

Treatment of Hepatitis C Infection

The cornerstone of HCV therapy is the capacity of treatments to achieve a SVR. Introduced in the early 1980s as a monotherapy, *interferon* (IFN) was found to be both poorly tolerated and poorly effective with a SVR in less than 10%. With *pegylated formulations of IFN* (Peg-IFN) optimizing its pharmacokinetics and combination with ribavirin for 48 weeks or longer, SVR rates increased to about 50%. During the decade 2000–2010, Mazzaro and colleagues first reported sustained clinical and virologic response in 44% of patients with HCV-CryoVas treated with *Peg-IFN* plus *ribavirin* for 12 months [34]. Saadoun and colleagues reported that the combination of *Peg-IFN plus ribavirin* compared with *IFN plus ribavirin* showed higher rates of complete clinical (67.5% vs 56.2%) and virologic (62.5% vs 53.1%) responses, regardless of HCV genotype and viral load [35].

However, the safety profile was not satisfactory, and such therapies often led to many severe adverse events, such as severe cytopenia, disabling fatigue, fever, and depression. In

addition, fatigue, arthralgia, and myalgia were frequently reported, which is a particular concern in rheumatic patients in whom distinguishing drug side effect from underlying disease was often difficult. Other autoimmune exacerbations, such as SS and systemic lupus erythematosus, have been reported after IFN treatments [36].

The Era of Direct-Acting Antiviral Therapy

In the last years, new oral, IFN-free regimens have been approved for the treatment of HCV infection. They have revolutionized the management of HCV infection, characterized by a dramatic efficacy leading to cure rates of 90–100% in all HCV genotypes, with minimal side effects and short duration (12–24 weeks) [37, 38]. Even in difficult-to-treat populations, including cirrhotic and previously treated patients, IFN-free DAA regimens have been reported to be very efficient. Numerous large prospective studies have been published with different DAA combinations, showing high antiviral potency [39].

For the treatment of *HCV-CryoVas*, the VASCUVALDIC study enrolled 24 patients (median age, 56.5 years; 50% cirrhotic) who received *sofosbuvir plus ribavirin* for 24 weeks. Seven patients also received immunosuppressive therapy: *rituximab*, *corticosteroids*, *and plasmapheresis*. Eighty-seven percent of patients were complete clinical responders, and SVR was obtained in 74% of patients at week 12 post-treatment [40].

Sise and colleagues reported a case series of 12 patients with HCV-CryoVas (median age, 61 years; 50% cirrhotic) treated with *sofosbuvir plus simeprevir* ($n = 8$) or *sofosbuvir plus ribavirin* ($n = 4$). Seven patients had evidence of renal involvement, including five patients with membranoproliferative glomerulonephritis. Four patients received rituximab concurrent with DAA therapy. An SVR at posttreatment week 12 was achieved in 83% of patients. Cryoglobulin levels decreased in most patients, with a median decrease from 1.5% to 0.5%, and disappeared in four out of nine cases [41].

Despite the unquestionable evidence of a viral cause and the obvious efficacy of antiviral treatments, immunosuppression remains a major treatment, especially in patients with HCV-CryoVas in cases of severe manifestations (renal, digestive, or cardiac involvements) or in patients with failure or contraindication to antiviral treatment. *Rituximab* (a monoclonal anti-CD20 antibody) targets activated B cells, which are responsible for cryoglobulin production and eventually CryoVas lesions. Randomized controlled trials showed that *rituxi*mab has better efficacy than conventional immunosuppressive treatments (i.e., *glucocorticoids*, *azathioprine*, *cyclophosphamide*, *or plasmapheresis*) or placebo [42, 43]. Two other controlled trials showed that the addition of rituximab to Peg-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [44, 45].

Considering the very rapid and potent virologic efficacy of new DAA combination and the proven correlation between SVR and clinical response, the exact place of rituximab, plasmapheresis, or other immunosuppressive drugs remains to be defined.

Corticosteroids, used alone or in addition to IFN, did not favorably affect the response of HCV-CryoVas manifestations in controlled studies [46]. Plasmapheresis, which offers the advantage of removing the pathogenic cryoglobulins from the circulation, should be considered for rapidly progressive glomerulonephritis or life-threatening involvements. Immunosuppressive therapy is usually needed in association with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis [47].

Conclusion

Arthritis should be considered as a manifestation induced by HBV and HCV infection. There is not a specific clinical pattern, although frequently resembles RA, with a nonerosive phenotype. True RA may be easily mistaken for HBV- and HCV-related polyarthritis, particularly in the early stages of the disease when erosions and rheumatoid nodules are usually absent. Nonsteroidal anti-inflammatory drugs, hydroxychloroquine, and low doses of corticosteroids are the cornerstones of the treatment of HBV- and HCV-related arthritis. For HCV infection, the introduction of DAA has revolutionized the management, characterized by a dramatic efficacy leading to cure rates of 90–100% in all HCV genotypes. Immunosuppressive therapies, such as azathioprine, cyclophosphamide, rituximab, and plasmapheresis, are recommended in cases of severe manifestations or in patients with failure or contraindication to antiviral treatment.

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Arthritis Associated with Alphavirus Infections: Chikungunya

11

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Abbreviations

BFV	Barmah Forest virus
CCL2	Chemokine (C-C motif) ligand 2
CHIKV	Chikungunya virus
CLIP	Cross-linking immunoprecipitation
CPE	Cytopathic effect
CTLs	Cytotoxic T lymphocytes
CXCL10	C-X-C motif chemokine 10
GM-CSF	Granulocyte-macrophage colony-stimulating factor
MAYV	Mayaro virus
NF-κB	Nuclear factor-kappa B
ONNV	O'nyong-nyong virus
RER	Rough endoplasmic reticulum
RRV	Ross River virus
SINV	Sindbis virus
VEEV	Venezuelan equine encephalitis virus
WEEV	Western equine encephalitis virus
WHODAS II	World Health Organization Disability Assessment Schedule, version 2

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Introduction

Alphaviruses are a genus of enveloped, single-stranded RNA viruses that belong to the *Togaviridae* family, along with other viruses like dengue, yellow fever, West Nile, and Zika. They are arboviruses, so called by the mechanism of transmission to humans: arthropod-borne viruses. All are transmitted in zoonotic cycles and have entered to human-human cycles involving *Aedes* spp. mosquitoes, *Aedes aegypti*, and occasionally, *Aedes albopictus* [1–4].

Alphaviruses are distributed around the world and produce diverse human diseases including febrile rash, encephalitis, and arthritis. They are classically referred to as "Old World" and "New World" viruses. "Old World" group includes viruses that are related to rheumatic diseases, and chikungunya virus (CHIKV) is the most relevant, but Ross River virus(RRV), Mayaro virus (MayV), O'nyong-nyong virus (ONNV), Barmah Forest virus (BFV), and Sindbis virus (SINV) can also produce occasional outbreaks [5–7]. "New World" viruses refer to the group of viruses that in the Americas had produced fatal encephalitic diseases, in which Venezuelan equine encephalitis virus (VEEV) and Western equine encephalitis virus (WEEV) are the most relevant [8, 9]. Although "Old World" and "New World" viruses are a public health concern, this chapter focuses only in "Old World" alphaviruses, mainly CHIKV. Since 2004 there is growing information regarding the association of alphaviruses and acute and chronic arthritis that has become a focus of research from the molecular, cellular, immunogenetics, clinical, treatment, and prevention. The chapter summarizes the most important evidence regarding these aspects.

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_11

Epidemiology of Arthritogenic Alpha Viruses

Alphaviruses are widespread across all continents and in general have the potential to disseminate because of the adaptations of vectors, especially to climate and climate change [10, 11]. Arthritogenic alphaviruses have been globally reported, and in the last two decades, the world has experienced large epidemics due to CHIKV, SINV, RRV, MAYV, and ONNV that produced a high public health and socioeconomic burden [2, 10, 12].

CHIKV is present around the world and is the most relevant arthritogenic alphavirus due to its capacity to generate large epidemics. This virus was isolated in 1952 in Tanzania (before Tanganyika), and the largest registered epidemic took place in 2004–2011 and was transmitted by *Aedes albopictus*. The epidemic that began in Kenya and spread across South East Asia reached an estimated 1.4–6.5 million cases. Italy was the first European country that reported autochthonous cases in 2007 and France in 2010 [3, 10]. Prior to 2013, the virus only circulated in Africa, Asia, Europe, and Australia. In December 2013, the first local transmission of CHIV was reported in Saint Martin island and thereafter spread to other countries, reaching almost all the continent in 2017 [13, 14].

RRV is an endemic virus of Australia and Pacific islands, where the most common is a widespread arboviral disease, causing thousands of cases each year [15]. In the last two decades, RRV outbreaks have increased in Australia, accounting for more than 70% of notifications of mosquito-borne diseases and generating a significant annual cost for the health-care systems. The increase of cases due to RRV has been attributed to many factors, including climate, mosquito density, and individual risk factors [16].

ONNV is an endemic virus for Africa. It was first identified in East Africa between 1959 and 1962 epidemics, in where more than two million cases were reported. After 1962, no more cases were documented, until it reemerged in Uganda in 1996, with attack rates ranging from 3% to 29%; more recent outbreaks have been reported in Liberia and Chad during 2003–2004 [17].

SINV is found in Europe, Asia, Africa, and Australia. In endemic areas, serologic prevalence can reach 39%. It was first isolated from mosquitoes during an epidemic of febrile illness in the district of Sindbis, Egypt, in 1952; the serological tests in cases of rash and arthritis suggested that SINV was the causative agent. In 1961–1962, it was isolated from human tissues (blood sample, skin). Although more outbreaks occurred in South Africa during 1963–1964, it spread to Europe in the same years, suggested by serological studies performed in Israel, Italy, and Finland. In 1974, another outbreak occurred in South Africa, Sweden, and Finland. In the last three decades, more outbreaks have occurred, mainly in South Africa and Northern Europe. The last outbreak was reported in 2013 in Sweden [18, 19].

MAYV is an endemic virus for South America. It was first identified during an outbreak of acute febrile illness in Trinidad in 1954. More outbreaks have been reported in Brazil, Bolivia, Venezuela, Surinam, Guyana, and Peru. The last outbreak registered occurred in Venezuela in 2010 [10, 20].

Immunopathogenesis of Arthritis Associated with Alphavirus Infections

Derived from the lessons of recent epidemics, especially those due to chikungunya in the Americas after 2013, the knowledge of pathogenesis of arthritis associated with alphavirus infection has evolved enough to better understand the mechanisms underlying chronic arthritis after CHIKV infection. The presence of new technologies such as deep sequencing has allowed the characterization of gene regulation involved in the control of infections and symptoms and the long-term immune response. However, despite all the existing information, there are still questions to answer, especially those related to the induction of autoimmune mechanisms that produce rheumatoid arthritis. Herein we summarize the most important findings focused on the pathogenesis of arthritis associated with alphavirus infections with emphasis on the virus and host factors [14].

Viral Factors

There are mainly three viral factors that could influence the development of arthritis associated with alphavirus infection: viral load, evasion of immune responses, and induction of autophagy. Viral load correlates with the presence and intensity of symptoms; the higher the viral load, the higher the organ damage. Studies are consistent that CHIKV-infected patients with higher viral loads developed chronic arthritic symptoms [21].

Evasion of immune responses is another mechanism by which the virus could be responsible for the development of chronic arthritis. In animal models, CHIKV can survive in macrophages for a long time using diverse mechanisms of evasion and establishing chronic infections [22]. Another mechanism of evasion of immune responses includes the neutralization of antibodies via genetic mutations or cell-to-cell transmission. For example, in CHIKV, there are strains that evade domains of neutralizing antibodies, inducing persistence of the virus and impeding clearance [23, 24].

Induction of autophagy has been observed in alphavirus infection, especially in CHIKV, which activates pathways of stress in organelles like endoplasmic reticulum with the consequent autophagy induction, enhancing the viral RNA replication [25]. This phenomenon observed also in other viruses like human immunodeficiency virus, mycobacterium, and parasites is due to the mimicry of viral proteins

with host protein motifs that interact with other proteins in pathways that conduce to an explosion of the cellular infrastructure [26, 27].

Host Factors

A recent meta-analysis reported that nearly 50% of patients that became infected with CHIKV did not recover fully after 3 months of infection [28]. Based on this data, it is logical to assume that not only the viral factors are involved in the immunopathogenesis of arthritis; there are many host factors that play a critical role in the resolution of symptoms or the progression of arthritic symptoms and development of chronic arthritis, including autoimmune arthritis. These factors include innate immune response, host proteins, adaptive immune response, osteoblasts, cytokines, chemokines, growth factors, and genetic factors, especially those related to the main histocompatibility complex [29].

After CHIKV enters the body through an infected mosquito bite, it reaches the dermic microvasculature; replicates primarily in leukocytes, the liver, and the spleen; and disseminates to other organs like muscle, bones, and synovial tissue, a situation that generates a rapid and intense inflammatory response that correlates with the symptoms of an acute phase of infection [14].

According to animal models, innate immune responses are the first line of defense. Monocytes, macrophages natural killer (NK) cells, and dendritic cells drive the initial response. There is evidence showing that arthritis is related to upregulation of gene associated with macrophage recruitment and activation, generating a cascade of inflammatory mediators, prostaglandins, and interleukins that results in tissue damage and arthritis [2, 30, 31]. Gardner et al. [32], who replicated an animal model of CHIKV-induced arthritis, demonstrated that infection of mice with two different isolates resulted in (1) development of clearly foot swelling that was preceded by mononuclear viremias and (2) prolific infiltrate of mononuclear cells in muscular tissues with the subsequent subcutaneous edema, clear signs of arthritis with lymphocyte infiltration, and disruption of synovial membrane.

The presence of monocytes, macrophages, and NK cells, as the main components of inflammatory infiltrate in animal models of alphavirus-induced arthritis, shows that innate immune responses play a role in the pathogenesis of arthritis. In fact, there is evidence showing that in patients with demonstrated alphavirus-induced arthritis, macrophages and NK cells can be isolated from synovial exudates [33].

It seems that the symptom generated by the acute viremia (first 5–7 days) is primarily controlled by innate immune responses through IFN-alpha/beta and with the participation of monocytes, macrophages, and NK cells. Once acute viremia and inflammatory responses generated by the virus and their products drop, the symptoms generally disappear; nevertheless, due to epidemics outcomes, almost all research is focused on investigating the mechanisms involved in the persistence of symptoms beyond the acute phase of the disease. At this time, it is not fully explained whether these chronic symptoms that are different in each patient and can last for months to years are due to host responses only or have a contribution from the virus intrinsic characteristics. There is evidence that supports that arthralgia and arthritis are due to inflammatory responses induced by virus replication within tissues after acute viremia, a situation that has been demonstrated at least for CHIKV. The mechanisms by which alphaviruses can persist for a long period in tissues despite strong T-cell and IFN alpha/beta responses seem to be related to the capacity of the virus to evade neutralization and T-cell responses through the shutdown of major histocompatibility molecules synthesis, a situation that limits antigen presentation [15, 22, 34].

On the other hand, host response to infection has been related to the persistence and progression of arthritic symptoms beyond the acute phase. Most studies have reported that there are pro-inflammatory cytokines secreted during acute and chronic phases that are the same with those associated with autoimmune arthritis, like rheumatoid arthritis, and one theory states that alphavirus infection could trigger autoimmune responses that could explain part of the clinical picture of some chronic arthritis observed in infected patients; nevertheless this is not a consistent feature on published reports [35, 36].

Studies that have focused on host responses instead of viral persistence conclude that immune responses could be the responsible factors of chronic arthritic symptoms. Diverse cytokine profile has been characterized in chronic symptoms after CHIKV infection like IL-6, IFN α/β, CCL2, GM-CSF, IL-7, IL-12, IL-13, IL-17, and CXCL10 upregulation that seems to be related to the persistence of symptoms. Although that information is growing, at this moment it is not consistent and coherent with the clinical evolution of patients [37, 38].

More recently, Chang et al. explored the differences in cytokine profile in acute CHIKV infection between patients with and without chronic arthritic symptoms and demonstrated that robust cytokine response during acute infection was correlated with less incidence of chronic joint pain. Although these authors found differences between cytokine response between subjects with and without chronic symptoms suggesting that cytokine response is necessary to clear the virus from the body, two important limitations are observed: (1) there were no serial measurements of cytokine profile to make multiple comparisons at different times to elucidate the relationship of chronic symptoms and cytokine serum levels; (2) the term "chronic arthritis" was used in patients who referred symptoms only by phone call instead of being evaluated in person to confirm or rule out the presence of true arthritis. This same group reported that there was no evidence of CHIKV virus in synovial fluid of patients with chronic arthritis suggesting that viral persistence

and local replication are not responsible for chronic arthritis and maybe host autoimmune response better explains the chronic symptoms and the response to immunomodulatory treatments [39–41].

To this regard, and trying to provide objective information about the rheumatic manifestations related to CHIKV infection on acute and chronic phase and taking into account the lack of objective information about the presence or absence of true arthritis after CHIKV infection, our group followed ten patients with confirmed CHIKV infection for 1 year (monthly visits) in an attempt to characterize clinically and biochemically the evolution from acute to chronic phase. We used objective tools like Disease Activity Index WHODAS II score to evaluate the self-reported disability, joint exploration to evidence synovitis, and serial measurements of inflammatory biomarkers and rheumatoid factors. In that study, we reported that more than 50% of patients persist with disability and arthritic symptoms beyond the acute phase; all patients presented elevation of inflammatory biomarkers in the acute phase, especially interleukin 6. Interestingly we observed positivity of rheumatoid factor in the acute phase in all patients, drop of levels over time in patients without chronic symptoms and persistence of positivity in patients with chronic symptoms, and persistence of high levels of interleukin 6 in patients with chronic symptoms. After 1 year of follow-up, no case was consistent with the diagnosis of rheumatoid arthritis (RA). Of those ten patients, two presented true arthritis after follow-up, and four presented only arthralgia. We consider that clinical evaluation, joint exploration, and serial measurements are essential to really define the presence or absence of true arthritis because of the implications in terms of classification and therapeutic approaches [42].

Genetic Susceptibility of Arthritis Associated with Alphavirus Infections

Genetic susceptibility of the host may play a critical role in both the infection and the development and progression of arthritic symptoms. Specific polymorphisms of the human leukocyte antigen (HLA) that is known to predispose subjects to develop autoimmune arthritis may be related with CHIKV-induced arthritis. The MHC class II alleles HLA-DRB1∗01:01 and HLA-DRB1∗04:01 are involved in the pathogenesis of RA by recognizing citrullinated peptides and consequently activation and clonal expansion of autoreactive CD4+ T cells [43, 44].

HLA CLASS I Disease Mechanism

HLA class I molecules present endogenous antigens, such as those derived from viruses and intracellular bacteria, for recognition by the immune system. This process involves ubiquitination of endogenous cytosolic proteins and then degradation into short 8–16 amino acid peptides, optimal for HLA class I binding. These are subsequently transported into the endoplasmic reticulum where they bind HLA class I molecules, before exiting the RER and being transported to the cell surface. HLA class I presented antigen is then recognized by CD8+ T cells and natural killer (NK) cells. Once CD8+ T cells become activated, functional effectors T lymphocytes (CTLs) are produced which possess lytic capabilities and also play a role in generating CD8+ T memory cells, acting as part of both the innate and adaptive immune responses. Activated NKs act before clonal expansion and differentiation of CD8+ T cells and compliment the CTL response. They act as one of the first lines of innate immune defense by producing cytokines, including interferons, which aid in the recruitment of additional cells to the site of inflammation and also produce cytokines and chemokines that have a cytolytic activity aiding cell destruction [45].

HLA class I molecules play a role in presenting endogenous antigens, including those derived from viruses, which have been proposed to be key triggers for arthritis. Viral antigens may trigger arthritis through molecular mimicry and via acting as superantigens. Molecular mimicry occurs when viral antigens that are similar to self-antigens activate autoreactive T-cells that can cross-react with self-antigen generating autoimmunity. Some viral antigens could also act as superantigens, producing a strong non-specific immune response that then cross-reacts attacking and damaging tissues in the body [46, 47]. Viruses can also alter HLA class I and II expression, potentially leading to greater antigen presentation to CD8+ T cells, with certain alleles more prone to viral manipulation. During viral infection soluble HLA levels, involved in regulating the immune response, have also been shown to be increased in RA patients, the level of which is dependent on HLA allele present.

HLA Class II Disease Mechanism

Exogenous peripheral antigens are internalized via antigen presenting cells (APC) and are degraded into 13–18 amino acid residue peptides, in the increasingly acidic compartments of the endocytic pathway. HLA class II molecules are synthesized in the rough endoplasmic reticulum (RER) where they associate with the invariant chain (Ii) to prevent endogenous peptide binding. The HLA class II molecule is then routed to the endocytic pathway, where it is degraded, leaving a short fragment of the Ii class II-associated invariant chain peptide (CLIP) bound, which is then exchanged for peptide. The HLA class II peptide complex is then transported to the cell surface for recognition by CD4+ Th cells, which determine whether an immune response is mounted. If

an immune response is mounted, CD4+ Th cells will activate naive B cells to produce antibodies, or in the case of self-antigens autoantibodies and aid in macrophage recruitment.

The highest-risk alleles, belonging to the DR4 group, have higher affinity to a polar residue such as T or S in the P6 pocket, where it can form a hydrogen bond with DR-β13H (histidine at 13th position of beta chain), while DR1 (and presumably DRB1∗0901 and ∗1001) prefer adenine over tyrosine or serine, possibly because the phenylalanine at DR-β13 makes the pocket more hydrophobic [43, 48]. Six of the alphaviruses known to infect humans carry T or S at pocket P6 suggesting a possible mechanism of disruption of tolerance. Of these, CHIKV is one with the highest serologic prevalent in humans and endemic in regions with high prevalence of DR4 alleles, such as Latin-American countries like Mexico and Ecuador [49, 50]. Host genetics haplotype HLA-DRB1∗11 and HLA-DRB1∗11-HLADQB1∗03:01 are associated with resistance to CHIKV infection, and HLA-DRB1∗04-HLA-DQB1∗03:02 are susceptible to CHIKV infection. Also, HLA-DRB1∗04 or HLADRB1∗01 alleles were present in 66.6% of CHIKV-infected patients with RA [28].

Table 11.1 Clinical manifestations of chikungunya fever

Virus	Alfavirus (RNA virus)
Vector	*Aedes aegypti* and *Aedes albopictus*
Incubation	3–7 days(1–12)
Appearance of symptoms	4–8 days (2–12)
The virus causes a febrile illness associated with	
Fever	Sudden +39 ° C 76–100% continuous or intermittent
Arthralgia/arthritis∗	(87%)
Back pain	(67%)
Headache	(62%)
Cutaneous rash	(50%)
Severe forms are rare; symptoms usually remit 7–10 days ∗Asymmetric intense and debilitating more frequently hands and feet, swelling associated with tenosynovitis	
Atypical manifestations	
Skin: hyperpigmentation, ulcers or aphthous, generalized erythema, vesicular-amphilophus lesions, desquamation of palms, vasculitis, liquinoid eruptions	
Lung: pneumonia	
Gastrointestinal: nausea and vomiting, acute hepatitis	
Neurologics: encephalitis, meningoencephalitis Guillain-Barre, cerebellar syndrome, mental confusion, convulsions	
Eyes: conjunctivitis, optic neuritis, episcleritis, rhinitis, uveitis	
Hematological: lymphadenopathy, thrombocytopenia	
Complication: Non-frequent Pain for months or years	

Clinical Manifestations of Alphavirus Infection

CHIKV infection could lead to fever, arthritis, encephalitis, myelopathy, peripheral neuropathy, myeloneuropathy, myopathy, and sometimes death. Chronic disorders post-CHIKV are nonspecific polyarthralgia, rheumatoid arthritis-like illness, undifferentiated inflammatory arthritis, soft tissue rheumatism, seronegative spondyloarthritis, or psoriatic arthritis (PsA) [28]. After incubation period (2–6 days), the symptoms begin as fever (more than 90%, lasting 1 week), myalgia (90% usually lasting between 7 and 10 days), polyarthralgias/polyarthritis (95%, lasting from weeks to months), and erythema (50%, 1 week). The chikungunya fever is divided into an acute phase (less than 10 days), subacute (between 10 and 90 days), and chronic (more than 3 months); the symptoms are continuous or relapsing-recurrent. Symptoms of subacute and chronic disease are distal polyarthritis, non-arthritic polyarthralgia, oligoarthritis in previously affected joints, subacute hypertrophic tenosynovitis, peripheral vascular disorders, depressive symptoms, fatigue, and weakness (Table 11.1) [42, 51, 52].

There are atypical manifestations of chikungunya fever, such as skin manifestations: hyperpigmentation, aphthous ulcers, transient nasal erythema, generalized erythema, vesicular-amphilophus lesions, desquamation of palms, vasculitis, lichenoid eruptions, renal failure that can be triggered by the use of non-steroidal anti-inflammatory drugs (NSAIDs), nephritis, pneumonia, nausea and vomiting, acute hepatitis (associated with the use of paracetamol or previous alcoholism), encephalitis, meningoencephalitis, Guillain-Barre, cerebellar syndrome, mental confusion, convulsions, conjunctivitis, optic neuritis, episcleritis, rhinitis, uveitis, lymphadenopathy, and thrombocytopenia [52, 53] (Table 11.1).

Chronic Arthritis

The clinical manifestation of rheumatic disorders post-CHIKV infection can be divided into three groups: (1) true arthritis, including seronegative and seropositive arthritis, (2) spondyloarthritis, and (3) undifferentiated polyarthritis. Arthralgia without arthritis is the most common manifestation of chronic inflammation post-CHIKV infection [53, 54].

According to carried out studies, arthritis is benign; however, between 10% and 30% arthritis can be persistent up to 3 years after infection and resembles RA and in some cases with the presence of positive rheumatoid factor, with bone erosions and presence of the human leukocyte antigen (HLA DR 04 and HLA DR 01) in a manner similar to that observed in RA. Because the cytokines secreted during CHIKV infection are the same found in RA, CHIKV may be considered to trigger the onset of RA in genetically predisposed individuals. However, it is necessary to demonstrate the presence and

participation of autoimmune processes in arthritis induced by alphaviruses [54].

Risk Factors for Chronic Arthralgia/Arthritis

There are some clinical factors and biomarkers associated with an elevated risk of progression to post-CHIKV chronic disease, such as older age, symmetrical distribution of arthralgia, initial severe joint pain, female gender, and previous osteoarthritis [55–61]. DAS-28 and WHODAS-II score at diagnosis have been associated with increased risk of progression to chronicity [42]. Some biomarkers have also been found as predictors of chronicity, e.g., high level of interleukin-6 and ferritin [42, 55].

Diagnosis

The diagnosis of alphavirus, especially CHIKV, is based on clinical, epidemiological, and laboratory criteria. However, CHIKV infection may be definitely confirmed only by laboratory methods such as detection of viral RNA or by identification of the specific anti-CHIKV antibodies [62–65]. The viremia of CHIKV lasts between 5 and 7 days and is the period in which IgM antibodies are detected 3–8 days after the symptoms and persist for 1–3 months. IgG is observed from 4 to 10 days after onset of symptoms and persists for years. Another method for diagnosis is molecular biology (real-time PCR). Some biomarkers have been investigated as predictors of chronicity, and it was found that in the initial phase the C reactive protein (CRP), the erythrocyte sedimentation rate (ESR) and interleukin-6 (IL6) were found increased. The ESR and IL-6 could predict chronicity from the moment of diagnosis [42]. The non-specific laboratory abnormalities observed during an early stage of chikungunya fever are leukopenia with lymphopenia, thrombocytopenia, or elevated aminotransferases levels [65] (Table 11.2).

Table 11.2 Diagnosis of chikungunya

Molecular and serological tests	Viral RNA: analysis with reverse transcription-polymerase chain reaction; RT-Anti CHIKV antibodies: ELISA IgG, IgM
Leukopenia	++
Neutropenia	+
Lymphopenia	+++
Thrombocytopenia	<100,000
VSG and C-reactive protein	Increased
Interleukin −6	Increased
+++High intensity: 70–100% of patients ++Medium intensity: 40–69% of patients ++Medium intensity: 10–39% of patients	

Treatment of Chikungunya Arthritis

During the acute phase of chikungunya, joint and muscle pain predominates, and analgesics and antipyretics are recommended: acetaminophen at a dose of 500–750 mg every 4–6 h, without exceeding the maximum daily dose of 4.0 g, due to the risk of hepatotoxicity. Tramadol hydrochloride 50–100 mg orally should be used every 6 h. In cases of severe pain, you can combine analgesics with opiates. Hydration and absolute rest are crucial components of the patient's integrative approach [66].

Pharmacological treatment in the chronic phase: the persistence of clinical manifestations for more than 3 months from the onset of symptoms is considered a chronic phase. Arthralgia is mild in some of these patients, which means that the disease is in true regression. On the contrary, in a percentage of patients (20–30%), intense inflammatory manifestations are observed, many of which adequately meet the criteria of the American College of Rheumatology to be classified as RA and the treatment must be with drugs modifying the disease such as hydroxychloroquine, methotrexate, sulfasalazine, and even biological therapy [67, 68]. However, there is little evidence of their efficacy from large clinical trials. Chopra et al. [69] studied the effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal and arthritis post-chikungunya; the results showed no advantage of meloxicam over the symptoms. Recently, the results of the combination of triple DMARDs therapy (methotrexate, sulfasalazine, and hydroxychloroquine) vs monotherapy with methotrexate in chronic persistent chikungunya arthritis were informed. The triple therapy was superior to monotherapy with hydroxychloroquine with a higher percentage of patients achieving EULAR clinical response and low disease activity. Nevertheless, none of the patent remission was observed [70]. Regarding biological therapy, there is a report of 21 cases of RA following CHIKV fever [71]. Based on the experimental model, there are some perspectives for future treatment of post-chikungunya chronic arthritis especially with biological therapy developed for rheumatoid arthritis, such as tocilizumab abatacept, tofacitinib, etc. [72].

Prevention

As in other diseases transmitted by mosquitos, it is important to have the following recommendations for the prevention of CHIKV [73]:

General Recommendations

- Wear clothes that cover most of the body
- Do not expose yourself to the bite of the mosquitoes

- Use mosquito repellent
- Use a canopy or cloth that covers your bed completely
- Install mosquito nets on doors and windows
- Prevent garbage from accumulating
- Do not leave containers where water accumulates
- Constantly wash water containers, as well as water tanks and cisterns
- Use larvicides in containers to eliminate mosquito larvae
- Use special insecticides to eliminate the mosquito in its adult phase

Vaccines for Chikungunya

Chikungunya fever has reemerged since 2004 to cause millions of cases. Because CHIKV exhibits limited antigenic diversity and is not known to be capable of reinfection, a vaccine could serve to both prevent disease and diminish human amplification during epidemic circulation. Owing to the lack of licensed vaccines and antiviral therapeutics, the primary response to CHIKV outbreaks is vector control. However, *A. aegypti* and *A. albopictus* populations continue to expand because of factors such as insecticide resistance and poor infrastructure, lack of education, and uncontrolled urban development. Thus, a vaccine still provides the best hope for limiting CHIKV infections and spread [74].

Vaccines as in other diseases constitute a fundamental pillar to eradicate these viral diseases; however, in these viral infections (dengue and chikungunya), they are not yet consolidated [75].

Perspectives

Chikungunya virus infection has been described so far in patients from 45 countries, including travelers. Therefore, this infection is considered an epidemic of acute disease, with low mortality, but with persistent and disabling chronic arthritis [76].

In addition to the clinical manifestations described previously, it is important to mention other extra-articular manifestations described in the early stages of the infection, such as myocarditis, cardiac arrhythmias, sepsis, and septic shock. During widespread CHIKV epidemics, excess mortality has been reported in newborns and the elderly [77].

In relation to the transition from acute to the chronic stage, it is important to mention that CHIKV RNA antigen has been found in the synovial tissue at 18-months post-CHIKV infection in a single subject [21]. In contrast, in 22 months after acute infection has not been identified CHIKV RNA or proteins in the synovial fluid of CHIKV arthritis patients suggesting that viral persistence may not be a requirement for persistent joint pain [40]. However, the analysis of the synovial fluid is different from that of the synovial membrane analysis. Therefore it is necessary to investigate the synovial membrane of these patients, in order to find evidences of CHIKV RNA.

Recently, a comprehensive review of the literature on CHIKV infection was conducted [78]. According to this review, the chronological analysis of epidemics of infection with this virus shows cycles of emergency and re-emergence of this infection on all continents. This is due to mutations in the viral genome that allows it to adapt to new vectors and survive at colder temperatures. Therefore the health authorities should remain alert to new outbreaks of CHIKV infection.

Vertical transmission of CHIKV infection has been described in humans. Evidence of CHIKV has been found in saliva and semen from infected patients. Therefore, the possibility of sexual transmission of CHIKV should be investigated [79, 80].

Importation into non-endemic areas of CHIKV infection by travelers returning from endemic areas is high risk. Epidemics can be controlled if health authorities take strict protection measures for travelers and develop vector attenuation programs. CHIKV should be suspected in returning travelers presenting with fever and severe polyarthralgia [81–83].

Regarding serological tests for viral infection, there is evidence of cross-reaction of CHIKV infection with other alphavirus antibodies; therefore, it is necessary to have a highly specific and sensitive test that is a gold standard to diagnose CHIKV infection [84, 85].

One of the most relevant aspects related to morbidity and mortality from this infection is the comorbidities of the patient who contracts CHIKV infection. It has been suggested that chronic diseases such as respiratory, cardiovascular, autoimmune diseases, diabetes, etc., present in the patient can be a risk factor to aggravate this infection and turn it into chronic infection [86, 87]. New studies will be needed to demonstrate the association between comorbidities and chronic CHIKV infection.

Atypical clinical manifestations of CHIKV infection have been described such as nasal skin necrosis, various forms of presentation of uveitis until reaching blindness, and acute disseminated encephalomyelitis. In relation to Guillain-Barre syndrome, an increase in this syndrome has been observed during an epidemic of CHIKV infection [88–91]. These changes in the clinical spectrum of CHIKV infection suggest an increase in virulence due to genetic mutations of the virus, more complete epidemiological and clinical reports, or the existence of Zika virus infection. In this regard, changes at the intra-host level, mutational of the E1 of the CHIKV, have been reported, which makes the virus more efficient and with greater capacity for dissemination by vector exchange [78, 92]. CHIKV and other Alphavirus infections are characterized by global inhibition of cellular

transcription and rapid induction of a cytopathic effect (CPE) in cells of vertebrate origin, causing changes in cell morphology, cell lysis, vacuolization, formation of syncytia, formation of inclusion bodies, etc. CHIKV is a highly pathogenic alphavirus representative because it has a nonstructural protein 2 (nsP2) that plays critical roles in both inhibition of transcription and CPE development. In this sense, a mutation of nsP2 has recently been identified that made CHIKV and its replicons incapable of inhibiting cellular transcription and dramatically this mutation decreases CPE. The mutations in nsP2 may be used for the development of new vaccine candidates against alphavirus infections [93].

One question to be clarified is whether CHIKV infection is a risk factor for developing rheumatoid arthritis (RA). A recent study suggests that in certain endemic regions, CHIKV infection may be one of the risk factors for developing RA [94]. These retrospective findings should be studied prospectively, analyzing the interaction between genes and environment that favors CHIKV infection. In this sense, a recent study shows that in early stages of CHIKV infection, the microRNAs of the skin fibroblast cells of mice and humans which are implicated in RA showed differential regulation in CHIKV infection [95]. Previously, Selvamani et al. [96] demonstrated that CHIKV enhances the replication in primary human synovial fibroblasts by modulating the miR-146a expression, suggesting that CHIKV suppresses the antiviral response by modulating the miR146a expression and downregulating the expression of NF-κB activation through a negative feedback loop. Both studies are relevant because they identify new biomarkers of CHIKV infection.

Conclusions

1. In the last 10 years, CHIKV infection has become a diagnostic and therapeutic challenge for rheumatologists from all over the world.
2. Due to the mutations described, the virus epidemic can appear anywhere in the world. Therefore, health authorities and first-contact physicians should be alert, especially in endemic areas where a new outbreak may occur.
3. The progression of an acute infection to the development of a chronic infection, characterized mainly by chronic arthritis, should be investigated, in order to identify both clinical and molecular progression factors to clarify if it is a chronic post-infectious arthritis or a persistent viral infection.
4. The patient with chronic arthritis should be treated by the rheumatologist using the necessary medications to reduce or if possible eliminate joint inflammation, improve the quality of life of the patient, and prevent the progression of disabling arthritis.
5. The interaction between the CHIKV infection (environmental factor) and the immunological/inflammatory response of the host, genetically determined, is the key to understanding the development of chronic arthritis after infection by the virus. These findings will allow the development of new preventive and therapeutic strategies to deal with outbreaks of CHIKV infection.

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Arthritis Associated with Alphavirus Infections: Dengue and Zika

12

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Introduction

Arboviruses cause diseases that occur epidemically, and many have a similar clinical expression at presentation. The genus *Flavivirus* of the family *Flaviviridae* consists of more than 70 members and includes dengue virus (DENV) and Zika virus (ZIKV). Until recently these viruses have not been directly implicated as a cause of chronic inflammatory arthritis or autoimmune diseases (AID) such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). However, they may either initiate rheumatic manifestations or trigger some AID via a variety of mechanisms or worsen an established AID. There are case reports and epidemiological studies that have established a relationship between DENV and ZIKV infection with the occurrence of arthritis and AID. Co-infection with chikungunya (CHIKV) may cause severe manifestations that in some cases may be fatal. These viruses cause their effects through numerous mechanisms interacting with host factors such as age, gender, genetics, previous infectious history, and immunocompetency.

ZIKV infection has been associated with complications like congenital microcephaly and fetal losses among women infected during pregnancy, as well as severe neurologic complications. Their syndromic expression can be either febrile (DENV or chikungunya) or exanthematic (ZIKV). Frequent symptoms at presentation are headaches, myalgias, arthralgias as occurring frequently in DENV infection (break-bone fever), arthritis in those with CHIKV co-infection, or both in those with ZIKV infection. Both DENV and ZIKV infections may overlap with other viral or bacterial infections, autoimmune diseases, or chronic conditions (e.g., diabetes mellitus, chronic heart failure, etc.) making the differential diagnosis very challenging. Hence, the practicing rheumatologist shall be equipped with appropriate knowledge of implicated viruses. Even though it is not an easy task, suspecting them on clinical grounds in individuals presenting with either typical or atypical clinical manifestations or living or coming from geographic areas where DENV and ZIKV are endemic is crucial [1].

Epidemiology

Currently five human epidemic mosquito-borne arboviruses, yellow fever viruses, DENV, West Nile virus, CHIKV, and ZIKV, have emerged in both hemispheres during recent centuries. However, this has not been the case for other mosquito-borne arboviruses (Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Usutu virus, Spondweni virus, O'nyong-nyong virus, and Rift Valley fever virus) that have only emerged in specific regions [2]. At least in 215 countries/territories, arboviral diseases are a global public health threat and are potentially suitable for the most important arboviral disease vectors with more than half of these regions reporting cases, and the increasing number of reports highlights the expansion of their common transmission vectors [3]. Dengue is widespread throughout the tropics, with risk factors influenced by local spatial variations of rainfall, temperature, relative humidity, degree of urbanization, and quality of vector control services in urban areas. Before 1970, only nine countries had experienced severe dengue epidemics. Today, the disease is endemic in more than 100 countries in World Health Organization regions (WHO's): WHO's African, Americas, Eastern Mediterranean, South-East Asia, and Western Pacific regions. The Americas, South-East Asia, and Western Pacific regions are the most seriously affected. It is likely that the actual numbers of dengue cases are underreported, and many cases are misclassified. WHO reported in 2018 that a recent estimate indicates that 390 million dengue infections occur

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_12

Fig. 12.1 Dengue risk in the Americas and the Caribbean. (1) Risk areas are shown on a national level except for where evidence exists of different risk levels at subnational regions. Areas that are too small to be seen on the regional maps are labeled in dark blue or light blue depending on their risk categorization. (2) Jentes et al. [66]. (Source: Centers for Disease Control and Prevention. Chapter 3. Infectious Diseases Related to Travel. Available at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/dengue)

every year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease), and that another study estimates that 3.9 billion people in 128 countries are at risk of infection with dengue viruses, figures highlighting the overwhelming epidemiological and economic burden in endemic countries [4]. ZIKV continues to spread geographically to and within areas where competent vectors are present [5]. As of March 10, 2018, there were 84 countries, territories, or subnational areas with evidence of vector-borne ZIKV transmission and 64 countries, territories, or subnational areas where the competent vector is established but with no documented past or current ZIKV transmission; 13 countries have reported evidence of person-to-person transmission of ZIKV. Thirty-one countries or territories have reported ZIKV-related complications including microcephaly and central nervous system (CNS) malformations suggestive of congenital infection, and 23 countries or territories have reported an increased incidence of Guillain-Barré syndrome (GBS) and/or laboratory confirmation of a ZIKV infection among GBS reported cases [5] (Figs. 12.1, 12.2, and 12.3).

DENV and ZIKV Transmission

The knowledge of transmission of DENV and ZIKV to humans is of paramount importance to assess and then to apply preventive and control measures with consideration given to the various modes of transmission of ZIKV. *Aedes (Ae.) aegypti* mosquito is the primary vector of DENV that is transmitted to humans through the bites of infected female mosquitoes. After virus incubation of about 4–10 days, the infected mosquito is capable of transmitting the virus for the rest of its life. Infected symptomatic or asymptomatic humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected with the DENV can transmit the infection (for 4–5 days to a maximum of 12 days) via

Fig. 12.2 Dengue risk in Africa and the Middle East. (1) Risk areas are shown on a national level except for where evidence exists of different risk levels at subnational regions. Areas that are too small to be seen on the regional maps are labeled in dark blue or light blue depending on their risk categorization. (2) Jentes et al. [66]. (Source: Centers for Disease Control and Prevention. Chapter 3. Infectious Diseases Related to Travel. Available at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/dengue)

Ae. mosquitoes after their first symptoms appear. The *Ae. aegypti* mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes, *Ae. Aegypti* is a daytime feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Ae. Aegypti* bites multiple people during each feeding period. *Ae. albopictus*, a secondary dengue vector in Asia, has spread to North America and more than 25 countries in the European Region, largely due to the international trade in used tires (a breeding habitat) and other goods (e.g., lucky bamboo). *Ae. albopictus* is highly adaptive and, therefore, can survive in cooler temperate regions of Europe. Its spread is due to its tolerance to temperatures below freezing, hibernation, and ability to shelter in microhabitats. ZIKV is primarily transmitted by the bite of the same mosquito that transmits DENV, CHIKV, and yellow fever in tropical and subtropical regions. These mos-

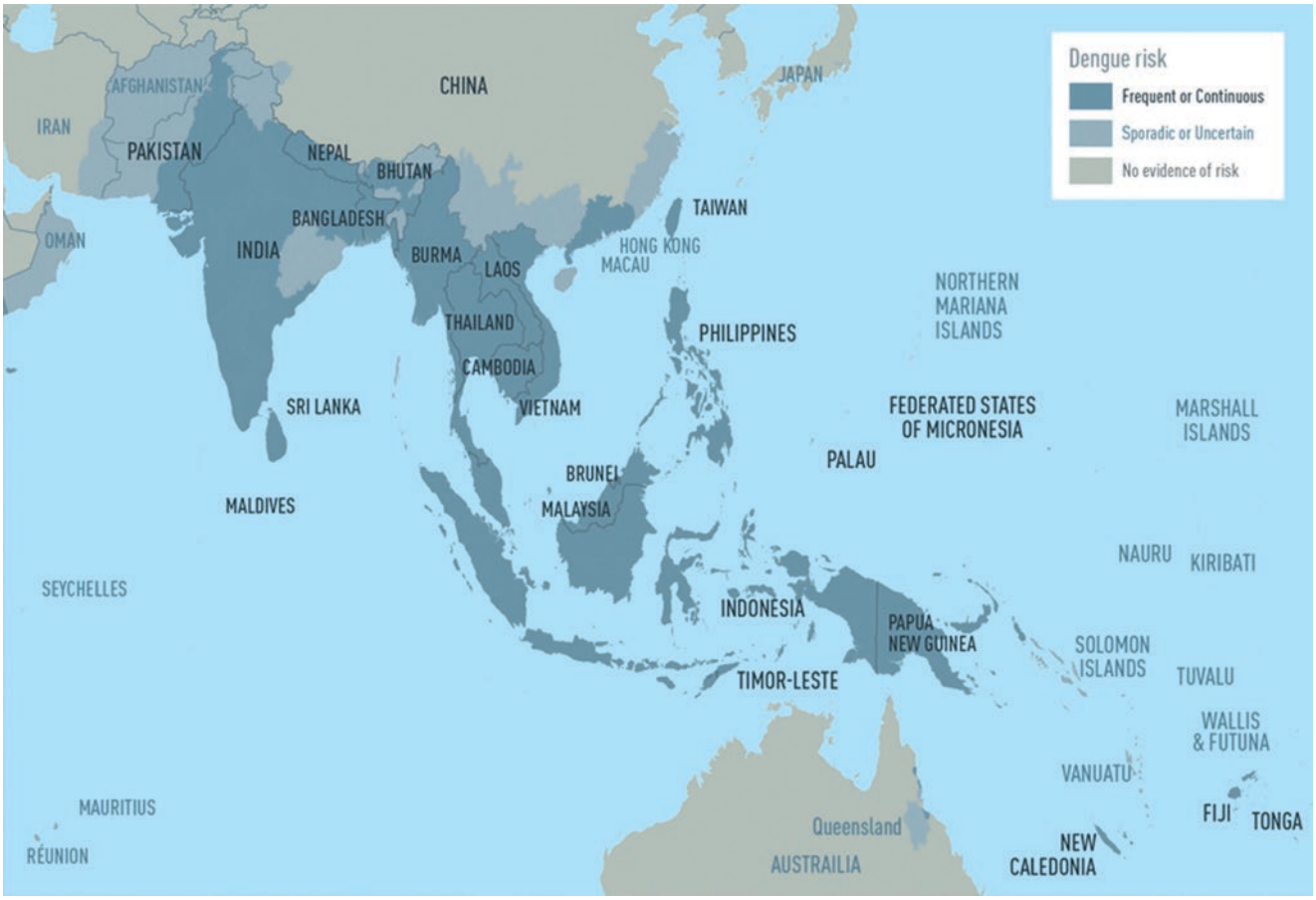

Fig. 12.3 Dengue risk in Asia and Oceania. (1) Risk areas are shown on a national level except for where evidence exists of different risk levels at subnational regions. Areas that are too small to be seen on the regional maps are labeled in dark blue or light blue depending on their risk categorization. (2) Jentes et al. [66]. (Source: Centers for Disease Control and Prevention. Chapter 3. Infectious Diseases Related to Travel. Available at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/dengue)

quitoes usually bite during the day, peaking during early morning and late afternoon/evening. Other transmission forms of ZIKV are maternal-fetal, sexual contact (vaginal, anal, and oral), blood products transfusion, organ transplantation, and laboratory exposure. ZIKV RNA has been detected in blood, urine, semen, saliva, female genital tract secretions, cerebrospinal fluid, amniotic fluid, and breast milk. After ZIKV infection ZIKV RNA may be detected after long periods of time [6]. It is possible that body fluids such as sweat or tears of patients with ZIKV disease could be infectious while the index patient's viral load is very high.

The Changing Nature of Global Health and the Influence of Environmental Changes on the Spread of DENV and ZIKV

Humans have influenced wild habitats by interacting and evolving with wild animals and plants; consequently, contemporary arthropods are frequently exposed to the modern human environment, domestic animals, and livestock to which they rapidly adapt. This adaptive process defined as domestication makes populations vulnerable to the threat of successive arbovirus epidemics. Most of the arboviruses are zoonotic, i.e., they infect a wide variety of arthropods, animals including birds in their sylvatic habitats, and humans as incidental hosts. Arboviruses have progressed to developed balanced relationships with the sylvatic hosts over many years which explains why morbidity and mortality are rarely observed in sylvatic animals when they are infected by arboviruses and is contrary to what happens with humans where infections by sylvan arboviruses are generally rare and balanced relationships have not been established; as a consequence, they will exhibit significant morbidity and mortality after infection by sylvan arboviruses. With the exception of epidemic arboviruses such as DENV, ZIKV, and CHIKV, human infections are generally not essential to maintain the arbovirus. Several factors have contributed to recent emergence and re-emergence of DENV, ZIKV, and CHIKV: increases in population density, development of global transportation systems, increased exposure frequency of humans to mosquitoes, and global mobility of humans. Other rapid

changes like an increased need of agricultural capacity, deforestation, and animal husbandry have also been implicated.

Pathophysiology and Immune Response

Viruses may cause arthritic manifestations by different mechanisms: (1) direct invasion (e.g., rubella), (2) immune complex formation (e.g., hepatitis B infection, alphaviruses, hepatitis C), or (3) by latent viruses and immune dysregulation (e.g., lentivirus infection). Viruses may initiate or precipitate rheumatic symptoms through mechanisms that depend on host factors (age, gender, genetics, infectious history, and immune response) and virus-related factors (virulence, etc.).

DENV and ZIKV are enveloped, positive-sense, single-stranded RNA viruses with a genome of approximately 10.7 kb in length that encodes a polyprotein with three structural proteins [capsid (C)-premembrane (prM)-envelope (E)] at the N terminus and seven nonstructural proteins (NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5) at the C terminus flanked by 5′ and 3′ untranslated regions (UTRs) [7]. There are four closely related but serologically distinct DENV types of the genus *Flavivirus*, called DENV-1, DENV-2, DENV-3, and DENV-4. There is transient cross-protection among the four types, which weakens and disappears over the months following infection; therefore, individuals living in a dengue-endemic area with all types co-circulating are at risk for infection with any and all DENV types. The virus-host interaction will determine the immune response. It is clear that there are DENV lineages that are more virologically and epidemiologically fit than others and are thus associated with more severe manifestations (DHF/DSS), whereas on the host side a prior DENV infection is the primary culprit associated with a more severe clinical picture. Although this also may apply to ZIKV infection where most infected people are asymptomatic or only develop a mild self-limiting febrile disease, there are fetal infection and congenital ZIKV syndrome and in adults ZIKV infection may induce Guillain-Barre syndrome (GSB), but unlike DENV, ZIKV is characterized by multiple modes of sexual transmission. Central to understanding mechanisms of viral immunity and pathogenesis is the knowledge of viral entry receptors and cellular tropism. Although the E protein has been known to mediate receptor binding and fusion, the precise identity of entry receptors for DENV and ZIKV in humans remains uncertain. DENV appears to use multiple cell surface molecules for binding to and infecting target cells, depending on the cell type. Several candidate molecules—including glycosaminoglycans; C-type lectins; dendritic cell-specific ICAM3-grabbing nonintegrin (DC-SIGN) and liver/lymph node-specific ICAM3-grabbing integrin (L-SIGN) (33–35); mannose receptor; the phosphatidylserine receptors T cell immunoglobulin and mucin domain (TIM) and Tyro3, Axl, and Mertk (TAM); and the phospholipid receptor CD300a—have been proposed to serve as receptors for DENV based primarily on in vitro studies with cell lines and primary human cells. One TAM family member, Axl, has also been implicated as a ZIKV entry receptor in studies with cell lines and primary human cells. Once the virus has invaded the cells, a short course of illness and self-limiting febrile symptoms in most DENV and ZIKV cases implicate a key role for the innate immune system in controlling DENV and ZIKV infections. The interferon system, comprising type I interferons (IFN-α, β), type II interferon (IFN-γ), and type III interferons (IFN-λ1–4), is the primary mechanism by which the innate immune system defends against viruses. Several lines of evidence indicate that the type I interferon system is the central mediator of protection against DENV and ZIKV. Mouse models of experimental DENV and ZIKV infection have shown that the interferon system is essential and more important than T and B cell-dependent immunity in controlling DENV infection in mice. All flaviviruses studied to date must evade the type I interferon system-mediated antiviral defense in order to replicate and cause disease in vertebrate hosts; thus, DENV and ZIKV employ multiple viral mechanisms to antagonize both type I interferon induction and type I interferon signaling, underscoring the importance of the type I interferon system in anti-DENV/ZIKV immunity. An innate immune response is triggered by the virus in infected primary human fibroblasts. Type 1 and type 2 interferons trigger the inhibition of Zika viral replication. At the molecular level, TLR3 recognizes the double-stranded RNA. Initial investigations suggested that at the cellular level the virus induces autophagosome formation to promote replication and may trigger apoptosis to foster viral dissemination.

Immune Cross-Reactivity Between Dengue and Zika Viruses

Serologic interpretation can be difficult in individuals who have resided in dengue-endemic areas, because of the significant serologic cross-reactivity between Zika virus and other flaviviruses, especially dengue viruses 1 through 4. Preexisting dengue antibodies due to past symptomatic or asymptomatic infection may yield false-positive Zika antibody results. Similarly, Zika virus antibodies also cross-react with DENV antibodies and may yield false-positive DENV antibody results. The four DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) and ZIKV are antigenically related mosquito-borne flaviviruses. The cross-reactivity between DENV and ZIKV has raised questions about cross-neutralization and concerns of cross-enhancement, yet few data exist characterizing the long-term antibody response. The extensive immunological cross-reactivity observed between ZIKV and other flaviviruses has practical implications for making serological diagnoses. Current serological methods are generally believed to not be

sufficiently specific to discern a ZIKV from DENV infection in the setting of secondary flavivirus exposure [8]. To address the degree and nature of cross-reactivity observed between DENV and ZIKV in serial specimens collected from study participants of three countries (Nicaragua, Sri Lanka and Thailand), Montoya et al. observed that among acute DENV infections and in the presumed absence of prior ZIKV exposure, cross-reactivity to ZIKV was observed following DENV infection, but DENV titers were consistently higher at all convalescent time points, a pattern that was observed in the antibody titers from all three countries, whereas that in acute ZIKV infections, a similar pattern was observed; DENV cross-reactivity was observed following ZIKV infection, but ZIKV titers were consistently higher at all convalescent time points [9]. Importantly, similar results were found when comparing ZIKV infections in the DENV-exposed and DENV-naive patients. ZIKV lies outside the DENV serocomplex, and the measurement of neutralizing antibody titers in convalescence can distinguish ZIKV and DENV infections when all viruses are analyzed simultaneously under similar testing conditions. For example, a patient with a ZIKV infection will be counseled and monitored differently than a patient with a DENV infection, given differences in common modes of transmission (e.g., sexual, maternofetal) and potential clinical complications. Given the antigenic similarity between ZIKV and DENV, the cross-reactivity of ZIKV and DENV B cell responses is not fully understood in the context of natural human infections. Andrade et al. used a novel ELISPOT-based assay designated Quad-Color Fluorospot that allows investigation of the DENV serotype specificity vs. cross-reactivity of the memory B cell (MBC) population at a single-cell level, adding a fifth color to include ZIKV [10]. They analyzed a unique set of peripheral blood mononuclear cells from the Nicaraguan Pediatric Dengue Cohort Study. Samples were collected ~2 weeks and several months after RT-PCR-confirmed ZIKV infection from children who were previously DENV-immune or DENV-naïve, and they also included a set of DENV patients who were ZIKV-naïve. Preliminary results showed that despite the antigenic similarity between DENV and ZIKV, MBCs from ZIKV-infected subjects were highly specific to ZIKV, with lesser cross-reactivity to DENV [10].

Diagnosis

Reverse-transcriptase polymerase chain reaction (RT-PCR) in serum is the main test for detection of viral nucleic acid of Zika, chikungunya, and dengue during the initial viraemic phase. The detection of Zika RNA in serum is limited to the first 5 days of the disease. Urine may be the specimen of choice to enlarge the window of detection of DENV and ZIKV after viremia has faded: PCR positivity is possible for a longer window, and higher viral loads facilitate virus typing. In dengue, ELISA can detect NS1 antigen in the acute phase, but this test was not yet available for Zika. Because viremia is short lived, a negative RT-PCR does not rule out Zika infection and serologic tests should be performed. Typically, IgM antibodies last for 2–12 weeks. In patients with clinical symptoms, the serum should be collected 4 days after disease onset and tested for Zika, chikungunya, and dengue. The applicability of IgM might depend on the clinical situation; the duration of anti-Zika IgM has not yet been established, and there are initial indications that anti-Zika IgM might be useful in diagnosing congenital Zika syndrome [11]. The sensitivity and specificity of IgM and IgG tests are poorly established, and there is strong cross-reactivity between ZIKV, DENV, and other flaviviruses. Plaque reduction neutralization tests (PRNT) can measure virus-specific neutralizing antibodies and may be able to determine the cause of the primary infection with high specificity and clarify cross-reacting results; however, PRNT is expensive and very labor intensive.

Clinical Manifestations Related to DENV and ZIKV Infections Including Arthritis and AID

It is estimated that over 390 million DENV infections occur yearly with 96 million being clinically apparent [12]. Rheumatic manifestations dominate the initial clinical manifestations of DENV infection. Adult DENV-infected patients have a higher likelihood of being symptomatic than children. The incubation period of DENV infection ranges from 3 to 14 days; symptoms typically develop between 4 and 7 days after the bite of an infected mosquito (Fig. 12.4). DENV infection consists of three phases: (1) a febrile phase, (2) a critical phase, and a (3) recovery phase [13]. In 1997, the World Health Organization (WHO) published a classification scheme with three categories of symptomatic DENV infection, dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), that was revised in 2009 by the same organization to introduce the following categories: (1) dengue without warning signs, (2) dengue with warning signs, and (3) severe dengue [13, 14]. The diagnosis of DENV infection should be suspected in febrile individuals with fever, headache, nausea, vomiting, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, positive tourniquet test, leukopenia, and a relevant epidemiologic exposure (residence in or travel within the past 2 weeks to an area with mosquito-borne transmission of dengue virus infection). ZIKV incubation's period is typically 2–14 days between mosquito bite and onset of clinical manifestations [15]. Clinical manifestations of ZIKV infection occur in 20–25 percent of individuals who usually develop a mild illness with symptoms subsiding within 2–7 days. Severe disease requiring hospitalization is uncommon, and case-fatality rates are reported to be low. It seems

that symptomatic infection has been described more frequently among women and patients <40 years in one study; however, neither female sex nor age was associated with an increased prevalence of infection [16]. Immunity to reinfection occurs following primary infection. Symptoms and signs of ZIKV infection typically include acute onset of low-grade fever (37.8–38.5 °C), pruritic rash (erythematous macules and papules on the face, trunk, extremities, palms, and soles), arthralgia (notably in the small joints of the hands and feet), and non-purulent conjunctivitis; clinical illness is consistent with Zika virus disease if two or more of these symptoms are present. Other commonly reported clinical manifestations are myalgia, headache, dysesthesia, retro-orbital pain, and asthenia. Relapse of symptoms in the absence of repeat exposure has been described. In children, ZIKV infection includes intrauterine infection (vertical transmission during pregnancy), intrapartum infection (vertical transmission at the time of delivery), and postnatal infection (transmission via mosquito bites). In general, clinical manifestations in infants and children with postnatal infection are similar to the findings seen in adults with ZIKV infection; however, arthralgia is difficult to detect in infants and young children and very importantly no developmental complications have been observed in otherwise healthy children with postnatal ZIKV infection. ZIKV infection has also been associated with congenital microcephaly and fetal losses among women infected during pregnancy, as well as neurologic complications. Table 12.1 shows salient features comparing DENV versus ZIKV infection.

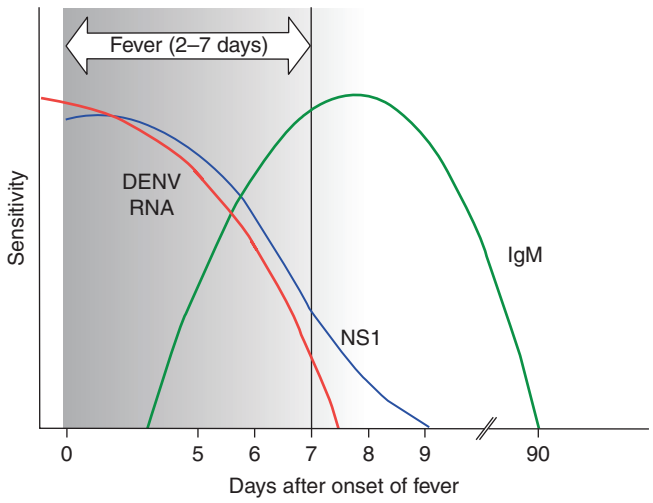

Fig. 12.4 Relative sensitivity of detection of dengue virus nucleic acid, antigen, and IgM. (1) DENV RNA and NS1 are detectable during the first week of illness. Anti-DENV IgM is detectable starting approximately 5 days after illness onset. Although most cases only have detectable IgM anti-DENV for 14–20 days after illness onset, in some cases it may be detectable for up to 90 days. Detection of anti-DENV IgG is neither sensitive nor specific in identifying patients with dengue. Abbreviations: DENV dengue virus, NS1 nonstructural protein 1. (Source: Centers for Disease Control and Prevention. Chapter 3. Infectious Diseases Related to Travel. Available at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/dengue)

Table 12.1 Comparison of salient features of a DENV versus a ZIKV infection

Features	DENV	ZIKV
Disease onset after infection	4–7 days	1–5 days
Disease duration (recovery)	6–7 days if only fever	4–7 days
Clinical manifestations		
Fever	Greater than 38 Celsius degrees	No or just mild fever
Headache	More common	Common
Itchiness	Common	Common
Rash	Common	Very common
Arthralgias	More common and severe pain	Common
Myalgias	More common	Common
Conjunctivitis	Not present	Very common
Laboratory findings		
Anemia and thrombocytopenia	Very common	None
Leukopenia	Very common	None
Increased C-reactive protein	Very common	Atypical
Elevated alanine-amino transferase	Very common	Atypical
Testing	*Acute infection:* (a) Reverse transcription-polymerase chain reaction (RT–PCR) from serum or plasma, cerebrospinal fluid, or autopsy tissue specimens during an acute febrile illness (b) Seroconversion from negative to positive IgM antibody to dengue (c) IgM antibody capture ELISA (MAC-ELISA) (d) Non-structural protein 1 (NS1) of DENV genome *Past DENV infection* (a) IgG ELISA *To determine the infecting serotype in convalescent sera* (a) Plaque reduction and neutralization test (PRNT) and the microneutralization PRNT	(a) Detection of Zika virus or Zika virus RNA or antigen in any body fluid or tissue specimen (b) Positive or equivocal Zika virus or dengue virus IgM test on serum with a positive titer for Zika virus (≥10) from plaque reduction neutralization testing (PRNT) together with negative PRNT titer (i.e., <10) for dengue virus

(continued)

Table 12.1 (continued)

Features	DENV	ZIKV
Tendency to severe hemorrhage (DFH)	Yes	No
Tendency to shock (if DFS)	Yes or no	No
Tendency to severe organ involvement	Yes	No
Sequelae	Linked to GBS, encephalomyelitis, and microcephaly	Linked to GBS, hemophagocytic syndrome, and encephalitis
Vaccines availability	Dengvaxia	DNA vaccine (GLS-5700)[a]
Mortality	2.5% mortality in hospitalized cases	Low estimated to be below 1%

[a]A phase 1, open-label clinical trial, a DNA vaccine elicited anti-ZIKV immune responses

Acute Manifestations Related to DENV and ZIKV Infection

Rheumatic manifestations are a major feature of DENV often overshadowed by other clinical features such as biphasic fever, skin rash, conjunctival involvement, pharyngitis, headache, vomiting, photophobia and orbital pain, lymphadenopathy, leukopenia, hepatosplenomegaly, and in severe cases DHF and/or DSS. Typically, DENV involves muscles, tendons, joints, and bones. Polyarthralgia is often present but eclipsed by intense backache and pain in the long bones. Severe myalgia is common and creatinine phosphokinase levels may be raised. Apart from joint and bone tenderness, there is little to find on joint examination. The diagnosis may be suggested by an acute viral type illness in a person from a DENV endemic area that requires serological confirmation [17]. While the basic constellation of symptoms including fever and rash is common to many arboviruses, including DENV, ZIKV, and CHIKV, there are some differences in symptomatology: conjunctivitis has been linked more commonly with ZIKV, severe arthralgias occur more commonly with DENV and CHIKV, and more prolonged arthralgias and rheumatological symptoms characterize CHIKV. Arthralgias occur frequently in DENV-affected patients (60–80%), but typical arthritis is seldom found; however, given the high frequency of DENV infection and its life-threatening consequences including 500,000 reported cases of DHF and DSS, its arthritic phenotype is still unknown. Patients experiencing various clinical forms of DENV infection behave phenotypically different. Few cases have been reported presenting possible DENV-related arthritis. Patil et al. reported the case of a 28-month-old Indian boy with fever of 5 days duration and black stools the day prior to admission with petechial lesions over the trunk and abdomen and an erythematous rash on palms and soles, tachycardia, a wide pulse pressure (50 mm Hg), and hepatomegaly. A diagnosis of DENV infection was made on a positive NS1 antigen and positive DENV IgM. He was treated as per standard WHO protocol with improvement and discharged home. On the 5th day, the patient was readmitted with a diffusely swollen right knee with restricted movements (radiograph of the right knee revealed widened joint space with normal surrounding structures). He had anemia, thrombocytosis, and ESR of 120 mm; ANA and CHIKV IgM antibodies were negative. Arthrocentesis of the right knee revealed turbid fluid with only five lymphocytes per mm^3 without any microorganism growth on cultures. Viral examination of the fluid was not performed and the Mantoux test was negative. A provisional diagnosis of DENV arthritis was considered against post-viral reactive arthritis because this patient did not have involvement of a hip joint. He was then treated with oral acetaminophen and at follow-up after 2 weeks of discharge was afebrile and playful without pain or swelling in the right knee [18].

Jayamali et al. from National Hospital of Sri Lanka in Colombo described a 14-year-old Sri Lankan girl who complained of right buttock and hip pain of 3 weeks' duration with confirmed DENV infection 10 days prior to the onset of symptoms [19]. Before the development of fever, arthralgia, myalgia, and headache approximately 5 weeks earlier, she was in good health. A nonstructural protein 1 (NS1) antigen test for DENV had been positive, and laboratory investigations were compatible with DENV. She was treated and had an uneventful recovery and was discharged after 6 days. Ten days after the onset of fever (4 days after the discharge), her right-sided buttock and hip pain recurred and needed to be readmitted to receive nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids with symptoms improvement and discharged home. Due to the persistence and worsening of her symptoms, she was readmitted. At exam, she did not have small or large joint pain involvement or swelling, and there was no history of enthesitis. She did not have red eyes, dysuria, skin eruptions, a diarrheal illness, or sore throat. There was no past history of joint pains, recurrent oral ulceration, or photosensitive rashes as well as no history of bloody diarrhea suggestive of inflammatory bowel disease. Her family history was unremarkable for arthritis or AID. There was no past or contact history of tuberculosis. A typical right sacroiliitis was demonstrated by radiograph with joint space widening and reactive bone changes, and MRI of her pelvis and sacroiliac joint confirmed acute sacroiliitis. ESR was elevated at 110 mm and her C-reactive protein was normal. DENV IgM on admission was positive. Human leukocyte antigen-B27, rheumatoid factor, antinuclear antibody, CHIKV antibody, hepatitis serology, Brucella serology, and tuberculin skin tests were all negative. She was treated with diclofenac sodium 50 mg every 8 hours and acetaminophen. She gradually improved with NSAIDs and her ESR reduced to 70 from 110 after 1.5 weeks of treatment, and physiotherapy was arranged at the local hospital as well as follow-up at regular intervals.

During the epidemic of 2006–2007 in Sri Lanka, Kularatne et al. compared the clinical and laboratory features of CHIK

and DENV confirmed cases based on serology at the General Hospital, Peradeniya, Sri Lanka [20]. During the study period, 54 serology confirmed patients with fever were included, of them, 21 patients had CHIKV infection, whereas 20 had DENV infection and 3 co-infections. The mean age of patients with CHIKV fever was 45 years (range 21–74 years), and patients with DENV fever was 30 years (range 15–63 years) (p = 0.005). Sixteen (70%) of CHIKV fever patients were females, while 15 (71%) of those with DENV fever were males (p = 0.007). Arthralgia was common to both groups (p = 0.155), while headache and a bleeding tendency were observed more in patients with DENV fever. Of CHIKV cases 12 (57%) developed acute arthritis compared with none in the DENV group (p = 0.001), lasting mean 6 days (range 1–14 days) and was a pathognomonic sign. Other clinical and laboratory features of patients with CHIKV and DENV were similar. In contrast to this study, Bhaskar et al. described the pattern of MSK manifestations among adults older than 18 years old with a confirmed serological diagnosis of DENV infection between April 2008 and December 2010 in Chennai, India. The study cohort included a total of 146 patients of whom 82 were men and 64 women with MSK manifestations occurring in 18 (12.3%) patients with a median symptom duration from onset to a resolution of symptoms of 5 days (range, 2–12 days). Only two patients had arthritis (one in the knee and one in the ankle with swelling and joint line tenderness without effusion) [21]. It seems that there are some features characterizing patients with CHIKV mono-infection and DENV + CHIK co-infection from those with DENV mono infection: high VAS score, morning stiffness, arthralgias, and restriction of joint movements. Patients with DENV mono infection had bone pains and myalgias in addition to joint pains; however, restriction of joint movements is only observed in 13.2% as compared with 100% of mono CHIKV or dual infection [22]. Between 2005 and 2010 individuals with a febrile disease from Peru, Bolivia, Ecuador, and Paraguay were enrolled in an outpatient passive surveillance study that aimed to estimate and compare the prevalence of non-hemorrhagic clinical manifestations of DENV infection by serotype. Detailed information on clinical signs, symptoms, and demographics were obtained. DENV infection was confirmed in patient sera with polyclonal antibodies in a culture-based immunofluorescence assay, and the infecting serotype was determined by serotype-specific monoclonal antibodies. Differences in the prevalence of individual and organ-system manifestations were compared across DENV serotypes. One thousand seven hundred and sixteen individuals were identified as being infected with DENV-1 (39.8%), DENV-2 (4.3%), DENV-3 (41.5%), or DENV-4 (14.4%). When all four DENV serotypes were compared with each other, individuals infected with DENV-3 had a higher prevalence of MSK and gastrointestinal manifestations, whereas individuals infected with DENV-4 had a higher prevalence of respiratory and cutaneous manifestations [23]. Similarly, Oliveira et al. examined the presence of arthralgia and/or objective arthritis among 251 patients with clinical and serological diagnosis (specific IgM detection by enzyme immunoassay) of exanthematous viral diseases; arthralgias but not arthritis were more common in patients with DENV (49%) and rubella (38.2%) than in those with human parvovirus (30%) and measles (28.1%), and except for measles cases, joint complaints were more prevalent in adults older than 15 years of age [24].

Other arboviruses like ZIKV and CHIKV circulate along with DENV and coexist in several endemic countries putting people exposed to them at high risk of developing viral-related arthritis, AID, or complications of a preexisting condition. Since 2015, Brazil has experienced a major public health crisis caused by the ZIKV, which is now considered endemic in all Brazilian states and is spreading widely in South and Central America and now threatens the USA and Europe. ZIKV and CHIKV share similar acute clinical presentation that may resemble commonest rheumatic disease manifestations. They may also complicate the clinical status of a rheumatic disease. Roimicher et al. from Brazil reported the case of a 53-year-old woman with a 4-year diagnosis of RA on clinical remission receiving stable dosages of prednisone (5 mg), etanercept (50 mg weekly), and methotrexate (20 mg weekly) 4 months before the development of fever (37.8 °C); a maculopapular rash on the face, trunk, and limbs; bilateral conjunctivitis; and polyarthritis involving the fingers, wrist, right knee, and ankles. ETN and MTX were suspended, and blood and knee synovial fluid (SF) were collected for molecular testing for ZIKV and CHIKV. Only ZIKV was identified in both samples by real-time PCR. The fever lasted 2 days, conjunctivitis 4 days, and rash and arthritis showed improvement on the 5th day. At day 7, all symptoms had disappeared, and a follow-up blood sample was negative for ZIKV by molecular test. DENV assays performed with a sample of that day were negative for IgM and positive for IgG (consistent with a prior DENV infection). Thirteen days after her first visit, the patient returned to the clinic, complaining of mild arthralgia and minor effusion of the right knee. New blood and SF samples were collected and tested for ZIKV and CHIKV. Again, only ZIKV was found in the SF, but it remained negative in the blood. ZIKV RNA fragments (843 base pairs) isolated from the patient's blood and SF samples were subjected to PCR sequencing, and no differences were found between them [25]. Arthralgias with a median duration of 3.5 days (range 1–14 days) have also been described at a varying rate (ranging from 14% to 65%) in previous outbreaks of ZIKV in Indonesia, Micronesia, French Polynesia, and Brazil, but none of these case series have reported longer-term rheumatological sequelae [26].

Another well-documented case demonstrated what can happen between the interaction of a healthy host and a concomitant ZIKV and CHIKV infection that may lead to MSK sequelae. Cherabuddi et al. described a 40-year-old woman who has travelled from the USA to Bogota, Colombia, for 7 days spending time outdoors in both urban and rural areas

and had had mosquito bites. During her stay she was asymptomatic but on day 3 upon returning to the USA developed scalp itchiness and fatigue, low-grade fever, and back pain on day 4. On day 5, she presented to the outpatient infectious diseases clinic with an erythematous scalp, a pruritic maculopapular rash on face and trunk that rapidly spread over the entire body. Her wrist and ankle joints became very painful and swollen, and she developed conjunctival redness. Saliva, serum, and urine samples were sent to the Florida State Laboratory as she fulfilled criteria for ZIKV testing. Reverse transcription–polymerase chain reaction (RT–PCR) tests for the viral genomic RNAs (vRNAs) of ZIKV, CHIKV, and DENV 1,2,3,4, and ELISA tests for ZIKV, CHIKV, and DENV IgM antibodies were performed, as well as an IgG assay for DENV. All the tests from the Florida State Lab were negative, with the exception of a positive RT-PCR assay for ZIKV vRNA. On day 9, she continued to have severe fatigue, worsening joint pain, and swelling, and because the DENV RT-PCR was negative, she was started on ibuprofen. The rash was significantly better but persisted on her torso and legs for another week. On day 16, she returned to work, though fatigue and joint discomfort persisted. Two months after the initial infection, she continued to experience severe arthralgias on wrists bilaterally and the plantar surface of the left foot and at the orthopedic clinic was noted to have tenderness of the second and third left metatarsal heads 3 months after the initiation of her illness. Radiographs of the left foot revealed no fractures or soft-tissue swelling, and thus she was recommended to wear a brace for 3 weeks. Five months after illness onset, she continued to have persistent pain, and an MRI study of the left foot showed trace fluid in the intermetatarsal bursae between the first and second metatarsal heads and second and third metatarsal heads. Persistence of symptoms prompted a re-evaluation of the viral isolation studies, which were initially terminated 9 days' post-inoculation upon isolation of ZIKV. It was noted that a second virus was present that displayed cytopathic effects (CPE) more consistent with findings expected for alphaviruses: lytic infection/apoptosis of infected. As described in CHIKV vRNA was detected in spent-cell culture media by using the CDC real-time RT-PCR for detection of CHIK virus. These findings highlight the need to consider CHIKV co-infection in patients with prolonged rheumatological symptoms after diagnosis with ZIKV and the usefulness of cell culture as an amplification step for low-viremia blood and other samples [27].

A 30-year-old man with SLE diagnosed at age 9, class III/IV lupus nephritis from 2007, and common variable immunodeficiency from 2014 who has become infected with both ZIKV and CHIKV during the 2016 outbreak in Rio de Janeiro, Brazil, with a protracted, severe disease, leading to a fatal outcome was documented by Silva et al. who initially presented with intense wrist and right ankle arthritis but no clinical manifestations of nephropathy; nevertheless, laboratory results showed a slight renal impairment with laboratory features showing anemia, leukocytosis with neutrophilia, lymphopenia, and elevated CRP. He was on prednisone, hydroxychloroquine, cyclosporine, colchicine, and prophylactic azithromycin. Previously he received irregular treatment with immunosuppressives and rituximab (2008–2010). Gonococcal infection was suspected, and ceftriaxone with azithromycin was used in addition to prednisone dose reduction and cyclosporine withdrawal. Blood cultures were negative and synovial fluid was not accessible by needle aspiration. Ultrasonography showed severe inflammatory joint disease with a high inflammatory response in his right ankle for which a synovial biopsy was indicated that showed fibro-adipose overgrowth, hypervascularization, and granulation with mono- and polymorphonuclear infiltrate and fibrin deposition. No bacterial, fungal, or *Mycobacterium tuberculosis* infections were detectable by direct examination or culture. Severe tenosynovitis was considered, and MRI of wrists and right ankle was performed 278 days post-symptom onset that showed bilateral wrists synovitis and tenosynovitis bilaterally. Coronal images demonstrated edema and excessive fluid in the carpus and radioulnar joints and in flexor and extensor compartments. A sagittal MRI diffusion-prepared weighted sequence with fat suppression image of the right ankle showed synovial overgrowth within the tibiotalar and intertarsal joints. Signs of plantar fasciitis and hyperintense abnormality were also observed (edema pattern). Patient's mother and sister had a history of non-laboratory proved CHIKV and ZIKV infection, respectively. ZIKV RNA and virus particles were detected in synovial tissue, blood, and urine and CHIKV RNA in serum sample, at the time of the diagnosis. Low level of IgG anti-DENV was also demonstrated. During the follow-up, ZIKV RNA persisted for 275 days post-symptom onset. The patient evolved with severe arthralgia/arthritis and progressive deterioration of renal function. Fatal outcome occurred after 310 days post-ZIKV and CHIKV co-infection onset. The data suggests a correlation between immunodeficiency and prolonged ZIKV RNA shedding in both blood and urine with progressive disease [28].

Contrary to the previous reports, Read et al. analyzed 7191 children enrolled in the Sentinel Enhanced Dengue and Acute Febrile Illness Surveillance System living in Puerto Rico on or before December 31, 2016, of whom 351 participants had a confirmed ZIKV infection; of them, 25 were infants (7.1%), 69 children (19.7%) aged 1–4 years, 95 (27.1%) aged 5–9 years, and 162 (46.1%) aged 10–17 years. Most patients (260 or 74.1%) presented for evaluation of ZIKV infection at fewer than 3 days after the onset of symptoms, 340 (96.9%) were discharged to home after evaluation, and 349 (99.4%) had fever, 280 (79.8%) had a rash, 243 (69.2%) had facial or neck erythema, 234 (66.7%) had fatigue, 223 (63.5%) had headache, 212 (60.4%) had chills, 206 (58.7%) had pruritus, and 204 (58.1%) had conjunctival hyperemia, but none of these patients developed ZIKV-related arthritis [29].

Chronic Manifestations

DENV and ZIKV have not been yet directly implicated as a cause of AID, but few case reports have signaled a possible association linking these viruses with AID. To investigate this risk, Li et al. conducted a population-based cohort study examining the Taiwan National Health Insurance Research Database that included 12,506 newly diagnosed DENV patients and 112,554 control subjects matched by age, gender, income, urbanization, and comorbidities between 2000 and 2010 with both cohorts being followed for a 3-year period to determine the incidence of AID. A Cox-proportional hazards regression analysis was applied to calculate the risk of AID between both groups. The DENV group showed an overall increased risk for 21 autoimmune diseases, with an adjusted hazard ratio (aHR) of 1.88 (95% confidence interval [CI], 1.49–2.37, $p < 0.001$). Compared with the control group, the DENV group had higher risks of Reiter's syndrome (as used by the authors) (aHR 14.03, 95% CI 1.63–120.58), multiple sclerosis (aHR 11.57, 95% CI 1.8–74.4), myasthenia gravis (aHR 5.35, 95% CI 1.43–20.02), autoimmune encephalomyelitis (aHR 3.8, 95% CI 1.85–7.8), systemic vasculitis (aHR 3.7, 95% CI 1.11–12.28), SLE (aHR 3.5, 95% CI 1.85–6.63), and primary adrenocortical insufficiency (aHR 2.05, 95% CI 1.25–3.35) [30].

Similarly, Monsalve et al. established an association between a ZIKV infection with Guillain-Barré syndrome (GBS) and with idiopathic thrombocytopenic purpura (ITP) in a small case-control study where the case group consisted of 29 Colombian patients with GBS associated with ZIKV infection, 13 patients with ZIKV and other neurological syndromes, and 53 patients with ZIKV without neurological conditions, AID, or first-degree relatives with AID, whereas the control group was composed of 100 healthy individuals with no evidence of ZIKV disease and without clinically AID. The association between rheumatic and thyroid autoimmunity in patients with ZIKV disease was evaluated using a panel of 14 autoantibodies related to these conditions. They have also performed a literature review on ZIKV infection and the presence of GBS and ITP. In contrast to what has been reported in the previous much larger study with DENV patients, Monsalve et al. found a lack of association of rheumatoid and thyroid autoimmunity with ZIKV disease. At the time of their literature review, 272 cases of GBS related to ZIKV were retrieved with the majority of these patients showing electrophysiological findings indicating acute inflammatory demyelinating polyneuropathy as the most frequent sub-phenotype (75.7%) and 24 cases of ITP in patients with ZIKV disease. Although a few fatal cases have been observed, most of the reported patients responded well to immunomodulatory treatment. They also speculated that molecular mimicry could be one of the mechanisms incriminated in the development of autoimmunity in ZIKV-induced diseases [31].

Several case reports have incriminated both DENV and ZIKV in an SLE phenotype. An association has been described by Zea-Vera et al. by a case report of ITP exacerbation with ANA positivity induced by ZIKV in a 30-year-old Colombian woman with prior history of ITP who presented with 2 days of headache, arthralgia, myalgia, and low-grade fever and a generalized erythematous rash. At the 4th day of symptoms, platelets dropped to 9×10^9/L without hemorrhagic manifestations that recovered to 30×10^9/L in 24 hours. They ruled out DENV as well as other viral infections. ZIKV was evaluated in serum and urine samples by a real-time reverse-transcriptase polymerase chain reaction that was positive in urine but negative in serum confirming a recent ZIKV infection with urinary tract virus excretion at 7th day after disease onset [32]. Talib et al. also reported a rare case of DENV triggering SLE and lupus nephritis (LN) during an outbreak of DENV during December 2012 in Maharashtra, India. DENV diagnosis was confirmed by the presence of NS-1 antigen during the first few days of fever. Eight weeks later, a kidney biopsy revealed lupus nephritis [focal proliferative and segmental sclerosis (stage IIIC)] [33]. Similarly, Rajadhyaksha and Mehra reported a case of a 22-year-old woman who presented with high-grade fever, skin rash, breathlessness, retro-orbital pain, abdominal pain, arthralgias, and myalgias for 10 days after DENV infection that evolved onto SLE and LN [34]. She tested positive for DENV IgM and received supportive treatment and was subsequently discharged. Four weeks later she developed recurrent fever, arthralgia, rash, and anasarca and found to have SLE and active LN (renal biopsy showed diffuse proliferative glomerulonephritis) with positive ANA, increased anti-dsDNA titers, and low complement levels. She responded to steroids and immunosuppressants. It is thought that DENV incites antibody production, which if excessive causes deposition of viral antigen-antibody immune complexes, leading to renal tubular damage and glomerulonephritis in susceptible individuals. DENV infection and SLE share common manifestations: fever, fatigue, arthralgia, rashes, leukopenia, thrombocytopenia, and serositis. Other cases of DENV infection either inducing or complicating a pre-existing SLE condition have also been reported; DENV infection may also mimic a lupus flare [35–39]. The misinterpretation of DENV infection serology may lead to the delay of the diagnosis of SLE [40, 41]. Zainal et al. have suggested that sera of patients with SLE may contain IgG together with other types of antibodies that can cross-neutralize DENV that may explain the rarity of severe dengue in individuals with SLE [42]. A variety of factors have been associated with macrophage activation syndrome (MAS): infections, drugs, and AID (SLE or systemic onset juvenile idiopathic arthritis). Morel et al. from Paraguay reported three pediatric cases that have developed AID related to a DENV infection. One was an 8-year-old boy who presented with confirmed DENV infection with persistent fever, proteinuria, hypoalbuminemia, leukopenia, throm-

bocytopenia, hypocomplementemia, and normal C3 and C4 levels, negative ANA, and dsDNA and lupus anticoagulant but IgM anticardiolipin antibody positivity. This patient improved without specific treatment. The other two patients, a 3-year-old boy and a 3-month-old boy developed MAS requiring intravenous bolus of methylprednisolone with clinical improvement and subsequent hospital discharge [43, 44].

Whether a DENV infection may worsen or not, an existing AID is always a consideration. Colman et al. in Paraguay [45] and Agüero et al. [46] in NW Argentina have addressed this question, the first by a retrospective, longitudinal observational study of patients with AID and DENV infection from February 2007 to February 2012. They examined baseline AID, AID activity, treatment, clinical classification of DENV severity, and patient outcomes during the acute phase of infection, 15–30 days post-infection, and 3 months after infection. They included 22 patients with SLE, rheumatoid arthritis, scleroderma, spondyloarthropathy, vasculitis, and anti-synthetase syndrome. Patient's AID activity at baseline was categorized as no activity ($n = 8$), low ($n = 11$), and moderate ($n = 3$). Sixteen patients were taking immunosuppressants and 16 corticosteroids, 3 of them at low doses. Half of the patients with DENV infection were classified as without alarm symptoms ($n = 10$) and the other half with alarm symptoms ($n = 11$). Only one patient had severe DENV infection. Eighteen patients (81%) had complete resolution of infection without worsening of baseline autoimmune disease, one had disease reactivation, and one had new organ involvement, which was a cerebrovascular accident in a RA patient. Complications related to DENV infection included thrombocytopenia with mucosal bleeding in a SLE patient with a favorable outcome and a central nervous system hemorrhage in a rheumatoid arthritis patient who died. Evaluation of AID 15–30 days post-infection revealed no activity in nine patients, baseline activity in nine patients, and exacerbation in one patient. Sixteen patients had been followed up at 3 months of which seven had no activity, seven had baseline activity, and two had SLE exacerbation: one hematologic and one cutaneous [45]. And the second study from Agüero et al. (February–May 2009) aimed to describe the clinical and biochemical features of consecutive patients with rheumatic diseases at three specific periods (pre-, during, and post-DENV infection). Demographic, clinical, biochemical, and overall assessment of rheumatic disease activity were ascertained as well as the use of medications. Eleven patients (nine women) were included: six with RA, two with SLE, and one with psoriatic arthritis, dermatopolymyositis, and ankylosing spondylitis, respectively, with an average age of 47 years. At the beginning of the DENV infection, all patients had fever and headache, and 90% exhibited leukopenia. Only the patient with SLE changed her clinical status during the DENV. There were no serious DENV events, but one patient had self-limited hepatitis. Glucocorticoids and hydroxychloroquine were not suspended [46]. Colman and Agüero had examined in their patients with an AID and concurrent DENV infection whether the intake of commonly used drugs to treat AID may predispose to severe forms of DENV infection or to lead to fatal outcomes. Currently the answer to this question has not been fully addressed yet by large longitudinal prospective studies including appropriate patient samples. However, these two small studies revealed that the vast majority of patients with AID did not have a worsening or reactivation after DENV infection from their baseline clinical status and the drugs used to treat them were not implicated. However, the refined study from de Abreu et al. analyzed the clinical profile and outcomes of patients with SLE and RA with primary DENV infection diseases reported to the Brazilian Health Information System with two aims: one to describe the clinical characteristics of RA/lupus patients who had dengue infection and one to compare RA/SLE patients with or without dengue for hospitalization rates after index dengue diagnosis for dengue-exposed or matching date for dengue-unexposed [47]. Sixty-nine SLE and 301 RA patients with DENV infection were included. In the RA/SLE with DENV case series, hospitalization was found in 24.6% of lupus subjects and of 11.2% of RA subjects. It differed by geographic region ($p = 0.03$), gender ($p = 0.05$), and use of azathioprine ($p = 0.02$). Dengue was the most frequent reason for hospitalization (43.0%). Hospitalization due to DENV was noted in 12 (42.9%) dengue-exposed patients ($p = 0.02$), while rheumatoid arthritis was reported as the cause of hospitalization in 22.2% of dengue-unexposed ($p = 0.005$). Five deaths were reported among the DENV-exposed and none among DENV-unexposed. Bacterial infection was the most frequent cause of death. DENV exposure was associated with an increased risk of hospitalization outcome in RA and SLE patients (RR = 6.2; 95% CI: 2.99–12.94). Comparing RA/SLE patients with or without DENV, DENV-exposed patients had an increased rate of hospitalization and death [47].

In patients with AID, a potential complication of immunosuppressive therapy is reactivation of pathogenic viruses that have remained latent (e.g., varicella-zoster virus, hepatitis B and C, Epstein-Barr virus) which have been more frequently seen in immunocompromised patients (RA or SLE) or in those on biologics. As numerous patients receive biologics while vacationing in countries where DENV is endemic, Deligny et al. conducted a survey among individuals who were experiencing a DENV infection and were on biologics; they described a case-series of eight patients of whom six were on anti-TNF agents and two on rituximab for a rheumatic condition. None of these patients experienced a severe DENV infection while on these agents [48]. A different approach was followed by Wu et al. [49] who studied the immunomodulatory effects of leflunomide in DENV-stimulated monocyte-derived dendritic cells (mo-DCs) and showed that leflunomide at therapeutic concentrations inhibited cytokine and chemokine production from DENV-infected mo-DCs by suppressing mo-DC maturation via downregulat-

ing of the expression of both CD80 and CD86. Leflunomide also inhibited DENV-induced mo-DC migration and mo-DC response to chemoattractants CCL19 and CCL21. Inhibition of mo-DC migration was likely due to the suppression of CCR7 expression on mo-DCs. These events were associated with the suppression of nuclear factor kappa B and activator protein-1 signaling pathways by leflunomide. Of note, only two patients in Colman et al. [45] and none in Agüero et al. [46] studies had taken leflunomide at the time of their DENV infection. The significance of leflunomide exposure among DENV-infected patients is uncertain, and we cannot conclude that this drug may have mitigated the clinical expression of DENV infection in those who have taken it [49].

Numerous other conditions have been related to DENV and ZIKV infection. Among them, neurological syndromes (involving both the peripheral and the CNS) are a hallmark of ZIKV infection. Mancera-Páez et al. described a 24-year-old woman from Cúcuta, Colombia, who developed the simultaneous occurrence of Guillain-Barré syndrome (GBS), plus MRI-demonstrated transverse myelitis (TM) and acute disseminated encephalomyelitis (ADEM+GBS) after an acute ZIKV infection confirmed by serum reverse transcriptase-polymerase chain reaction (RT-PCR) and convalescent ZIKV IgG antibodies. Interestingly, she had preexisting immunity against CHIKV and DENV. This patient survived with residual flaccid paraparesis after intensive care treatment, respiratory support, steroids, and intravenous immunoglobulin. The authors reviewed 19 cases of ZIKV-associated TM, encephalitis, and ADEM, and they occurred after a mean latent period of 10.5 days (range 1–96) post-infection. Although GBS and ADEM are usually considered post-infectious and associated with the development of antibodies against peripheral nerve and CNS epitopes, the authors speculated that the case of ADEM+GBS is para-infectious, induced by acute ZIKV neurotropism boosted by active immunity against other arboviruses [50]. DENV neurological complications seem to be sporadic and include meningitis, encephalitis, stroke, acute disseminated encephalomyelitis, and GBS [51]. The latter has been described in a 60-year-old Sri Lankan man who presented with a history of fever, arthralgia, and generalized malaise of 2 days duration with leukopenia, thrombocytopenia, and positive NS1 antigen and DENV IgM. He had weakness of both lower limbs, which progressed in an ascending pattern to involve upper limbs and neck muscles and to require assisted ventilation. Electromyography confirmed a demyelinating polyneuropathy, and cerebrospinal fluid showed albumin cytological dissociation. He was treated with intravenous immunoglobulins and made an uneventful recovery. Another neurological rare entity associated to DENV infection was longitudinal extensive transverse myelitis in a 15-year-old boy who presented with symptoms of transverse myelitis that developed 4 weeks after fever. MRI confirmed the diagnosis of longitudinally extensive transverse myelitis involving dorso-lumbar cord. After 6 weeks of corticosteroids and supportive management including physiotherapy, he recovered almost completely with minimal residual neurological deficit. Complications of possible CNS vasculitis and cranial nerve palsy due to DENV infection have been also described. One is a 53-year-old previously healthy Singhalese woman who developed acute-onset slurring of speech and ataxia with altered sensorium 1 day after recovery from a critical period of DHF with investigations revealing encephalopathy with brainstem ischemic infarctions considered to be compatible with CNS vasculitis. She was treated successfully with intravenous steroids and had a full functional recovery. The second patient was a middle-aged Singhalese woman who had otherwise uncomplicated DENV infection and developed binocular diplopia on day 4 of fever. The ocular examination revealed a convergent squint in the left eye with lateral rectus palsy but no other neurological manifestation [52–54]. Another infrequent DENV-associated manifestation is necrotizing scleritis that was described in a 60-year-old Japanese female with positive IgM and IgG for DENV infection who presented by slit lamp examination of her left eye conjunctival and scleral injection, elevation of the entire circumference of the sclera, and bulging of the sclera on the nasal upper side with a patch of avascular episcleral tissue. Additional systemic examinations identified no autoimmune diseases. She received intensive systemic and topical steroids during the initial acute phase that was tapered off over the ensuing 15 months as scleritis gradually declined. Overall there was no recurrence of active scleritis, but gradual thinning of the sclera continued to occur during the 18-year follow-up [55].

Assessment and Management of Pregnancy in a Possible Scenario of an Autoimmune Condition With ZIKV Infection

Pregnancy has long been considered a high risk for women with SLE and in other AID. The relationship between ZIKV and pregnancy related-complications is well established; thus, appropriate assessment and management of both conditions require deep knowledge on how ZIKV may impact both pregnancy and fetal outcomes given the insidious nature of ZIKV infections and its devastating consequences on fetal development. The practicing rheumatologist should know that the diagnosis approach is different in pregnant compared with nonpregnant individuals as ZIKV RNA persists approximately three times longer in a pregnant woman's serum and because of the offspring's risk of major CNS anomalies with congenital infection, even in an asymptomatic mother. The risk for vertical transmission exists throughout pregnancy and in offspring of both symptomatic and asymptomatic mothers, and the frequency of birth defects resulting from vertical transmission is also uncertain, but the greatest risk of serious fetal/newborn sequelae during exposure to ZIKV infection seems higher on the first or second trimester, but serious fetal/newborn sequelae may also occur on a third-

trimester infection. The severity of maternal symptoms and signs, maternal virus load, and preexisting DENV antibodies do not appear to be predictors of infant outcome. Major findings of 14 studies with adequate radiological assessment of suspected or confirmed Zika virus-infected fetuses found that the most common abnormalities among 66 fetuses were ventriculomegaly (33%), microcephaly (24%), and intracranial calcifications (27%) [56]. In the context of a planned pregnancy, a patient with an AID preconception assessment should include:

1. Assessment of disease activity and major organ involvement.
2. Presence of a hypercoagulable state and any other comorbidity that may impact on pregnancy outcomes.
3. Obstetric outcomes should be reviewed, with particular attention paid to history of small for gestational age fetus, preeclampsia, stillbirth, miscarriage, and preterm birth.
4. It will be wise to determine maternal antibody status including antiphospholipid (aPLs), anti-Ro, and anti-La antibodies.

ZIKV and DENV may induce autoantibody production with certain autoantibodies that will increase obstetric risks (recurrent pregnancy loss, stillbirths, preeclampsia, and neonatal lupus). Low-dose aspirin has been given to pregnant women to reduce the risk of preeclampsia and its sequelae (e.g., fetal growth restriction) regardless of the presence of aPLs; however, caution should be exerted in ZIKV-infected patients as DENV may co-exist. Maternal treatment of ZIKV is similar to those without pregnancy. The use of NSAIDs should be avoided until DENV infection has been ruled out to reduce the risk of hemorrhage and also be avoided in pregnant women ≥32 weeks of gestation to minimize risk for premature closure of the ductus arteriosus.

Women who are already pregnant or planning a pregnancy shall be advised to follow specific protective measures:

1. Avoid travel to a ZIKV-affected area (Fig. 12.5).
2. Avoid *sex with a partner who may be infected with ZIKV or who has recently travelled to a ZIKV-affected area* (use a barrier method of birth control every time).
3. *Adherence to workplace safety rules (if working at healthcare setting).*

Traveler type	**Country category**			
	Outbreak (red)	**Current or past transmission but no current outbreak (purple)[1]**	**Mosquito present but no reported cases (yellow)[2]**	**No mosquito (green)[3]**
Pregnant women	Do not travel.	Talk to a health care provider about potential risks. If you decide to travel, prevent mosquito bites and sexual exposure to Zika.	Prevent mosquito bites.	No Zika precautions recommended.
Women planning pregnancy	Talk to a health care provider about potential risks. If you decide to travel, prevent mosquito bites and sexual exposure to Zika. If traveling without male partner, wait 2 months after return before becoming pregnant.			
Men with a pregnant partner	Prevent mosquito bites. Use condoms or do not have sex for the rest of the pregnancy.			
Men with a partner planning	Prevent mosquito bites. Use condoms or do not have sex for at least 3 months after return.			

Fig. 12.5 Zika travel recommendations by traveler type and country category. (1) These countries have a potential risk of Zika, but we do not have accurate information on the current level of risk. As a result, detection and reporting of new outbreaks may be delayed. (2) Because *Aedes aegypti* mosquitoes (the mosquitoes that most commonly spread Zika) are present in these countries, Zika has the potential to be present, along with other mosquito-borne infections. Detection and reporting of cases and outbreaks may be delayed. (3) No *Aedes aegypti* mosquitoes (the mosquitoes that most commonly spread Zika) have been reported in these countries. However, other *Aedes* species mosquitoes have been known to spread Zika, and these may be present. (Source: Centers for Disease Control and Prevention. Zika Travel Information. Available at https://wwwnc.cdc.gov/travel/page/zika-travel-information)

4. *Blood donation has to be delayed for at least 4 weeks and umbilical cord blood donation avoided.*
5. *Those women* who are about to *get pregnant with donated sperm shall discuss with the appropriate experts.*

Transmission of Zika virus through breastfeeding has not been described, although the virus has been detected in breast milk. Women with Zika virus exposure may breastfeed. Recent reports have highlighted that chloroquine (CQ) is capable of inhibiting ZIKV endocytosis in brain cells, but this use is not indicated [57].

Prognosis

Morbidity and mortality of DENV are recognized to be high. Stanaway et al. estimated DENV mortality, incidence, and burden for the Global Burden of Disease Study 2013 by modelling incidence from officially reported cases and adjusted the raw estimates for under-reporting based on published estimates of expansion factors. They analyzed 1780 country-years of mortality data from 130 countries, 1636 country-years of dengue case reports from 76 countries, and expansion factor estimates from 14 countries. Their estimates were as follows: 9221 dengue deaths per year between 1990 and 2013, increasing from a low of 8277 (95% uncertainty estimate 5353–10,649) in 1992 to a peak of 11,302 (6790–13,722) in 2010. This yielded a total of 576,900 (330,000–701,200) years of life lost to premature mortality attributable to dengue in 2013. The incidence of dengue increased greatly between 1990 and 2013, with the number of cases more than doubling every decade, from 8.3 million (3.3 million–17.2 million) apparent cases in 1990 to 58.4 million (23.6 million–121.9 million) apparent cases in 2013. When accounting for disability from moderate and severe acute dengue, and post-dengue chronic fatigue, 566,000 (186,000–1,415,000) years lived with disability were attributable to dengue in 2013. Considering fatal and non-fatal outcomes together, dengue was responsible for 1.14 million (0.73 million–1.98 million) disability-adjusted life-years in 2013 [58]. Shepard et al., using the latest DENV incidence estimates from the Institute for Health Metrics and Evaluation's Global Burden of Disease Study 2013 and other data sources to assess the economic burden of symptomatic DENV cases in the 141 countries and territories with active DENV transmission, have estimated cases and costs by setting, including the non-medical setting, for all countries and territories from the scientific literature and regressions performed [59]. Their global estimates suggested that in 2013 there were a total of 58.4 million symptomatic DENV infections (95% uncertainty interval [95% UI] 24 million–122 million), including 13,586 fatal cases (95% UI 4200–34,700), and that the total annual global cost of DENV illness was US$8.9 billion (95% UI 3.7 billion–19.7 billion). The global distribution of DENV cases is 18% admitted to hospital, 48% ambulatory, and 34% non-medical. Similarly, on May 5, 2016, the WHO re-profiled ZIKV as a serious disease 1 year after the ZIKV outbreak in Brazil as a serious condition with enormous medical, ethical, and economic implications [60, 61].

Vaccine Development

Vaccine development is underway to protect from ZIKV. Several inactivated vaccine candidates have been found to induce detectable neutralizing antibodies in phase I trials [62]. The tetravalent dengue vaccine (CYD-TDV) was licensed in several Latin American countries and Southeast Asia but not in the USA beginning in 2015, and it was approved for use in Europe in 2018. CYD-TDV should be administered only to individuals with a history of previous dengue virus infection or laboratory evidence of previous dengue virus infection. In December 2017, the WHO issued a statement indicating that the vaccine is protective against severe DENV for individuals with seropositive DENV at the time of first vaccination but the risk of severe DENV is significantly increased for individuals with seronegative DENV at the time of first vaccination [63]. In April 2018 WHO advised that the vaccine should not be used until prior dengue infection can be confirmed at the time of administration [64].

Prevention

Until vaccines become completely efficacious and safe, avoiding mosquito bites continues to be the most important step and limiting travel to endemic areas when possible, control of mosquito populations, and together with the measures delineated to prevent ZIKV transmission in order to avoid its impact on fetal outcomes [65].

Decision-Making for the Practicing Rheumatologist

Urban crowding, ceaseless international travel, and immigration, human behaviors causing perturbations in ecologic balance will lead to innumerable infectious agents to emerge. The burden of both DENV and ZIKV infections remains underestimated and undermanaged and are associated to considerable suffering, increased health-care costs, disability, and mortality. In response to the threads and shared features of arboviral diseases, integrative medicine and innovative research to expand the understanding of the complex ecosystems in which these viruses evolve to initiate epidemics and to solve world pandemics need combined efforts that include the rheumatologist. Its unique training and

perspective in diagnosing and managing complex conditions will be of help to diagnose, manage, and diminish the suffering and economic burden of viral-related arthritis. A combined clinic including the rheumatologist and infectious disease specialist may also be of benefit as well as training physicians in both specialties. In the event of a patient with fever and joint pain, the rheumatologist's suspicion of DENV and ZIKV infection is of paramount importance, and the history intake shall always include:

1. Ascertainment of a recent travel to an endemic area
2. Immunocompetency (e.g., RA or SLE)
3. Use of disease-modifying antirheumatic drugs (traditional and biologics including small-molecules)
4. Demographic factors such as age and sex
5. Sexual history and pregnancy status
6. Exposure history such as work-related activities and those including different modes of transmission of ZIKV as described

Table 12.2 Clinical approach to a patient with high suspicion of DENV and ZIKV infection (after other viral-related arthritides have been considered and ruled out)

Clinical suspicion at presentation based on: (a) Fever (b) Rash (c) Joint pain
History intake: (a) Recent travel to an endemic area (b) Immunocompetence (c) Current use of traditional or biologic DMARDs (d) Socio-demographic factors (e) Sexual history (f) Pregnancy status (g) Exposure to work-related activities as performs of ZIKV transmission (h) Constitutional symptoms
Physical examination (a) Establish the presence of *febrile phase* (b) Carefully determine the presence of petechiae or mild bleeding (c) Is a rash present? Establish distribution (d) Is arthritis present? If present, establish arthritis location, duration, severity, and pattern (e) Look for warning signs (e.g., hypotension, tachycardia, etc.) (f) Do not miss the *critical phase* in DENV infection: shock, severe hemorrhage, and severe organ involvement
Testing: (a) Adhere to current serologic algorithms to screen and diagnose DENV and ZIKV
Other procedures: (a) Perform synovial fluid analysis (b) Synovial biopsy if indicated (c) Body fluids (e.g., urine) if indicated to detect DENV, ZIKV, and co-infection with CHIKV
Management: (a) Is mainly supportive (b) The rheumatologist must exercise judicious decision-making

Once DENV and ZIKV have been considered as a possible diagnosis, looking for the presence of the following signs and manifestations is mandatory:

1. Arthralgia versus arthritis. If present, pattern of arthritis
2. Fever
3. Rash
4. Constitutional symptoms
5. Organ involvement

After DENV and ZIKV have been highly regarded as the cause of a patient's illness, the rheumatologist shall collaborate with an infectious disease specialist and adhere to serologic algorithms to screen and diagnose these conditions. The rheumatologist shall never avoid synovial fluid and biopsy together with body fluids analysis (e.g., urine) if indicated. DENV and ZIKV infection management is mainly supportive, and the rheumatologist must exercise judicious decision-making. The clinical approach to a patient with high suspicion of either DENV or ZIKV is depicted in Table 12.2. Epidemiological surveillance to examine whether DENV and ZIKV are putative factors inducing either chronic arthritis or AID is necessary.

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Ebola Virus Disease Musculoskeletal Manifestations

13

Tochi Adizie and Adewale Adebajo

Background

Ebola virus is a single-stranded RNA virus that resembles rhabdoviruses (e.g., rabies) and paramyxoviruses (e.g., measles, mumps). There are actually five distinct species of Ebola virus (Zaire, Sudan, Tai Forest, Bundibugyo, and Reston) [1]. Epidemics of Ebola virus disease are generally thought to begin when an individual becomes infected through contact with the tissues or body fluids of an infected animal. Once the patient becomes ill or dies, the virus then spreads to others who come into direct contact with the infected individual's blood, skin, or other body fluids. Studies in laboratory primates have found that animals can be infected with Ebola virus through droplet inoculation of virus into the mouth or eyes, suggesting that human infection can result from the inadvertent transfer of virus to these sites from contaminated hands [2]. Sexual activity is also a recognized route of transmission [3]. In 2014, West Africa and the rest of the world was hit by a devastating outbreak of Ebola virus disease (EVD) that developed into a health crisis that left three countries gravely affected. Travel-associated cases were reported in Nigeria, Mali, and Senegal, and beyond Africa in the USA, UK, Italy, and Spain. Over 28,000 cases of Ebola Virus Disease were reported in the 2014–2016 West Africa outbreak [4]. Musculoskeletal complaints are common among survivors of EVD and can have clinical impacts beyond 2 years post-convalescence [5].

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The Effects of Ebola on the Immune System

Within hours of Ebola binding to macrophages, even prior to evidence of viral replication, there is significant macrophage activation and release of proinflammatory cytokines. These in vitro observations correlate with significant measured serum elevations in macrophage-derived cytokines, including IL-1β, TNF, IL-6, IL-15, IL-16, and IL-8 [6]. Elevated levels of autoantibodies against dsDNA are present in humans surviving EVD infection [7]. The data indicate that both polyclonal stimulation of B cell and secretion of autoantigens rather than antigen mimicry are involved in EVD induced autoimmunity. Levels of autoantibodies against dsDNA are generally higher during the acute phase of infection and decline above background during the convalescent phase [7]. Additional studies are needed to determine whether disease severity correlates with autoantibody induction in Ebola survivors.

Symptoms and Signs

The classical acute presentation of Ebola virus disease consists of fever, severe headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, and unexplained hemorrhage [8]. These normally occur after an incubation period of 3–8 days [9]. Increasingly, the concept of a post-Ebola syndrome is recognized. This entity appears to cause significant sequelae, with musculoskeletal complaints being among the commonest. In fact, in a recent large cohort study in Guinea, the most frequent symptoms in Ebola survivors were musculoskeletal pain (38%), headache (35%), abdominal pain (22%), ocular disorders (18%), and depression (17%) [10]. These symptoms can be present up to 2 years post-infection [10]. Observations indicate a pattern of arthralgia that is typically symmetrical involving multiple joints, most frequently affecting knees, back, hips, small joints of the hand, wrists, neck, shoulders, ankles, and elbows [10]. The incidence of post-Ebola rheumatic symptoms seems to increase with

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_13

older age, in line with other viral arthritides [11]. The majority of patients with Ebola-related rheumatic disease report early morning stiffness, with a median duration of 60 minutes in the Guinea cohort [10]. However, joint pain has also been noted to worsen with activity in some patients [11]. The level of pain is typically moderate to severe with a median score on the joint pain visual analog scale (VAS) of 60 mm reported by patients in the aforementioned cohort from Guinea [10]. Myalgias and muscle weakness are also common, and when accompanied by a rise in CK, can mimic an inflammatory myopathy. This is more a feature of acute infection, and there have even been cases of rhabdomyolysis documented in this context [12]. Periarticular structures are also affected in Ebola-related musculoskeletal disease. In addition, enthesitis and tendon ruptures have been observed [11]. In fact, when the enthesitis affects the shoulders and hips and is associated with inflammatory eye disease, this post-Ebola syndrome can mimic a spondyloarthropathy, although it is worth noting that sacroiliitis is uncommon. Costochondritis is frequently seen, however. Finally, sicca symptoms have also frequently been reported in Ebola survivors [10]. Clinical examination rarely demonstrates joint swelling, redness or warmth, although tenderness may sometimes be elicited. Functional limitation is often absent and corresponding X-rays are normal. There have been very few cases of active synovitis noted in the literature. An EVD survivor, in a follow-up clinic of 166 survivors in Freetown, Sierra Leone, presented with a proximal interphalangeal joint effusion of the left hand without a previous history of trauma or rheumatic disease. No changes on X-ray were noted. Joint swelling was present for 3 weeks and resolved with empiric antibiotic treatment [13]. Another report details synovitis and effusion of a knee joint in a survivor from Sierra Leone 34 days after disease onset [14]. There have, however, been several cases of inflammatory arthritis induced by Ebola vaccines in clinical trials. In one trial, 22% of patients exhibited vaccine-induced arthritis or arthralgia [15]. A third of this cohort also had axial disease. Acute-phase reactants were not elevated, HLA B-27 prevalence was not increased, and no elevation in auto-antibodies was observed. Arthralgias were self-limited, lasting on average 11 days and occurred around 10 days post vaccination. In this study, the vaccine was comprised of a live-attenuated recombinant vaccine consisting of the vesicular stomatitis virus (VSV) combined with a strain of Ebola. Detection of rVSV RNA in the synovial fluid suggests the presence of rVSV-Ebola in affected joints, as reported following rubella infection or vaccination. However, no replication of rVSV-Ebola could be demonstrated. The most likely hypothesis is, thus, that rVSV-ZEBOV-induced arthritis is associated with immune-complex deposition rather than by the virus itself causing inflammation to the synovium directly. One thing that is not clear at present is whether the severity of initial disease relates to a higher likelihood of having musculoskeletal symptoms in the convalescent phase. IgG antibody titers were significantly higher in 29 survivors of EVD with arthralgias than in those without after the 1995 outbreak in Kikwit, Democratic Republic of Congo, a finding consistent with persistent immune activation as the pathogenic mechanism [16]. We know that Ebola virus persists in certain sites such as the eye and the semen after recovery and that disease can recur in these sites [17]. The same has not been established for joint disease. In the case of the aforementioned patient from Sierra Leone with the knee arthritis [14], the synovial fluid tested negative for Ebola infection.

One further point to explore with the high prevalence of musculoskeletal complaints in Ebola survivors is the huge psychological burden of disease and its impact on physical well-being and symptoms. Indeed, there is a high prevalence of widespread tender pain points in those Ebola survivors who report musculoskeletal complaints. The post-Ebola syndrome has been linked to symptoms of depression and generalized anxiety and it is plausible that this aspect of the syndrome could contribute to the pain syndromes that survivors experience [18].

Laboratory Diagnosis

Patients with acute Ebola virus disease typically develop leukopenia, thrombocytopenia, and serum transaminase elevations, as well as renal and coagulation abnormalities. Other laboratory findings include a marked decrease in serum albumin, hypoglycemia, and elevated amylase levels. Proteinuria is a common finding, and renal insufficiency with elevated urea and creatinine can be seen in both the early and late stages of the disease. Patients may also develop significant electrolyte disturbances (e.g., hyponatremia, hypokalemia, hyperkalemia, hypomagnesemia, and hypocalcemia) secondary to the gastrointestinal manifestations of the disease. Diagnostic tests for Ebola virus infection are principally based upon the detection of specific RNA sequences by RT-PCR in blood or other body fluids. Viral antigens can also be detected using immunoassays. Ebola virus is generally detectable in blood samples by RT-PCR within 3 days after the onset of symptoms; repeat testing may be needed for patients with symptoms for fewer than 3 days duration [19]. A negative RT-PCR test that is collected ≥72 hours after the onset of symptoms excludes Ebola virus disease. A rapid chromatographic immunoassay (ReEBOV) that detects Ebola virus antigen can provide results within 15 minutes [20]. This assay can be useful to support a provisional diagnosis based on clinical examination and exposure history. However, the use of the ReEBOV assay alone could result in inappropriate admissions of uninfected persons to Ebola treatment units or fail to detect patients who are early in the

disease course. It is worth noting that isolation of Ebola virus in tissue culture is a high-risk procedure that can be performed safely only in a few high-containment laboratories throughout the world.

Differential Diagnosis

The differential diagnosis is extensive and includes several of the febrile illnesses that travelers to the west and/or central Africa are at risk of. Among these are malaria, Lassa fever, typhoid, meningococcal disease, influenza, measles, and Marburg hemorrhagic fever. Malaria, in particular, can occur concurrently with Ebola. Although a careful history including a history of contact exposure together with a thorough clinical examination is important, accurate diagnosis will ultimately depend on appropriate laboratory tests.

Treatment

Experience from the West African epidemic suggests that several concurrent strategies should be employed to prevent the spread of the Ebola virus. During acute illness, strict infection control measures and the proper use of personal protective equipment are essential to prevent transmission to health care workers. Supportive therapy with attention to intravascular volume, electrolytes, and nutrition is crucial [19]. In addition, individuals who have been exposed to the Ebola virus should be monitored so they can be identified quickly if signs and symptoms develop. Treatment guidelines by rheumatological societies, specifically for the musculoskeletal manifestations of Ebola, are lacking. Paracetamol is sufficient in most cases with opiate analgesia occasionally required [21]. Warm compresses also have a role. Typically NSAIDs are avoided as the first line due to the risk of hemorrhagic complications; however, there has been a reported case of inflammatory arthritis associated with recurrence of Ebola that was treated successfully with a combination of Diclofenac 50 mg BD and IM Methylprednisolone 80 mg [14]. If significant symptoms persist after 7–10 days of NSAID treatment and no other treatable cause is identified, stop NSAIDs and consider corticosteroids. Since corticosteroid use can result in overwhelming infection with the helminth *Strongyloides stercoralis*, some authors advise empirically treating patients in endemic areas for possible underlying *S. stercoralis* infection, before starting prednisolone, with one dose of Ivermectin 200 micrograms/Kg orally [21]. DMARDSs are rarely needed, though Sulfasalazine has been posited as an option for inflammatory arthritis refractory to simple analgesia and steroids [22]. Psychological counseling or pharmacotherapy for mental health disorders is often warranted.

Prognosis

Lasting or damaging arthritis does not so far appear to be a feature of EVD, though long term data are lacking, and require collecting.

Conclusion

In conclusion, musculoskeletal complaints are common among survivors of EVD and can have clinical impacts. Although patients with Ebola-related musculoskeletal disease report high pain scores, synovitis is uncommon. Simple analgesia is sufficient for treatment in most cases, but occasionally non-steroid anti-inflammatory drugs (NSAIDs) and steroids are required. Lasting or damaging arthritis does not so far appear to be a feature of EVD, though long term data are lacking, and require collecting.

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Parvovirus-Related Arthritis

14

Martin Brom and Carlos Edgardo Perandones

Abbreviations

ACPA	Anti-citrullinated protein Antibodies
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
CRP	C Reactive Protein
CSF	Cerebrospinal Fluid
EI	Erythema Infectiosum
ESR	Erythrocyte Sedimentation Rate
FM	Fibromyalgia
HBoV	Human Bocavirus 1 to 4
HLA	Human Leukocitary Antigen
INF-γ	Interferon γ
IL	Interleukin
IUT	Intrauterine Transfusion
JIA	Juvenile Idiopathic Arthritis
kD	Kilo Dalton
NIHF	Non-Immune Hydrops Fetalis
OA	Osteoarthritis
ORF	Open Reading Frame
PCR	Polymerase Chain Reaction
PPGSS	Papular Purpuric Gloves and Socks Syndrome
PRCA	Pure Red Cell Aplasia
PV-B19	Parvovirus B19
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
$sPLA_2$	Secreted Phospholipase A_2
STAT3	Signal Transducer and Activator of Transcription 3
TAC	Transient Aplastic Crisis
TGF-β	Tissular Grow Factor β
TNF-α	Tumor Necrosis Factor α

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History

Erythema infectiosum, or fifth disease, is known since 1889 when Tschamer described it as a variant form of German measles or rubella [1].

Although several epidemics have been described during the twentieth century, it was not until 1966 that the association of this febrile exanthematous disease and synovitis was described by Ager et al. in an epidemic in Port Angeles, Washington [2].

In 1975, Cossart et al. described Parvovirus B19 (PV-B19) in human serum [3] while comparing three commercially available tests for Hepatitis B against electrophoresis. They found small virus-like particles different from Hepatitis B in the sera of nine healthy blood donors, a patient with acute hepatitis and a patient that was a kidney transplant receptor. These new small particles resembled other known parvovirus by morphology, size, and density. When they studied samples drawn 2 weeks later from 4 of these patients, they found that all of them lost the antigen and became antibody-positive. They also found that at least 30% of the healthy blood donors presented antibodies against this newly described virus. They could not associate at that time any known disease to this virus. One of the serum samples containing this parvovirus-like particle was coded as Panel B and number 19 (Parvovirus B-19).

Thereafter, different clinical syndromes have been associated with PV-B19. The first association was suggested in 1981 when a parvovirus-like agent was detected in patients with sickle cell anemia that developed aplastic crisis [4, 5].

It was not until 1983 that Anderson et al. demonstrated that Parvovirus B19 was the etiologic agent of the fifth disease in an outbreak of erythema infectiosum in north London [6]. In 1985, in the same issue of the Lancet, White et al. and Reid et al. described the association between synovitis and PV-B19 infection [7, 8]. Then, several clinical syndromes have been found to be due to Parvovirus B19 infection, and will be described later in this chapter (Table14.1). Another important milestone in its history was the discovery of the

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_14

Table 14.1 B19 associations

Blood	Aplastic Anemia [4, 5]	
	Anemia in HIV/AIDS [179]	
	Leucopenia [180]	
	Thrombocytopenia [180]	
	Hemophagocytic Syndrome [181]	
	Kikuchi's Disease [182]	
	Thrombotic Thrombocytopenic Purpura [35]	
	Idiopathic Thrombocytopenic Purpura [183]	
	Autoimmune Neutropenia [184]	
	Autoimmune Hemolytic Anemia [185]	
Rheumatic	Arthritis [7, 8]	
	Adult-onset Still's Disease [110]	
	Systemic Lupus Erythematosus [79, 186]	
	Juvenile Idiopathic Arthritis [93]	
	Vasculitis	Schönlein-Henoch Purpura [187]
		Polyarthritis Nodosa [97]
		Systemic Necrotizing Vasculitis [98]
		Kawasaki Disease [102, 188]
	Fibromyalgia [103]	
	Chronic Fatigue Syndrome [189]	
	Carpal Tunnel Syndrome [190]	
	RS3PE [191]	
	Uveitis [112]	
	Systemic Sclerosis [192]	
	Myositis [193]	
Cutaneous	Erythema Infectiosum (Fifth Disease) [6]	
	Papular-Purpuric "Gloves and Socks" Syndrome [44]	
	Angioedema [194]	
	Livedo Reticularis [31]	
	Erythema Multiforme [32]	
	Vesico-Pustular Skin Eruption [33]	
Kidney	Acute Post-Infectious Glomerulonephritis [195]	
	Thrombotic Microangiopathy [129]	
	Collapsing Glomerulopathy [196]	
Liver	Acute Hepatitis [197]	
	Chronic Hepatitis [198]	
	Fulminant Hepatitis [199]	
	Hepatitis Associated Aplastic Anemia [200]	
Heart	Acute Myocarditis [201]	
	Chronic Myocarditis [202]	
	Dilated Myocardiopathy [203]	
	Myocardial Infarction [204]	
Neurologic	*Central Nervous System*	Encephalopathy [205]
		Encephalitis [206]
		Aseptic Meningitis [207]
		Stroke [208]
		Seizures [209]
		Chorea [210]
		Cerebellar Ataxia [211]
		Transverse Myelitis [212]
		CNS Vasculitis [155]
	Peripheral Nervous System	Brachial Plexus Neuropathy (Neuralgic amyotrophy) [213]
		Guillian-Barre Syndrome [214]
Fetus	Non-immune Hydrops Fetalis [215, 216]	
	Fetal Death [215, 216]	
	Severe Fetal Anemia [217]	
	Thrombocytopenia [218]	
	Myocarditis [219]	
	Hepatitis [216]	
	Ocular Injuries [220]	
	Brain Lesions [221]	

PV-B19 receptor in 1993. Brown et al. demonstrated that PV-B19 binds to the antigen of the blood-group P system or globoside [9].

Parvovirus B19: Microbiologic and Molecular Features

Parvovirus B19 is a member of the genus Erythrovirus of the family Parvoviridae. It has the typical characteristics of this family; it is a non-enveloped virus, with single-stranded DNA of 5.6 Kb and long inverted terminal repeats in both ends of the genome, which form imperfect palindromes. Its DNA has either a positive or negative polarity and an icosahedral nucleocapsid about 18–25 nm in diameter [10]. During replication, either the positive or negative strand can be covered by the capsid, unlike autonomous parvovirus, where only the negative strand is covered.

The viral capsid has 2 structural proteins, named VP1 (84 kD) and VP2 (58 kD). Both are encoded by the same Open

Reading Frame (ORF) (Fig. 14.1), and VP2 results from an alternatively spliced transcript. VP1 differs from VP2 only in an N-terminal extension of 227 amino acids called the unique region (VP1u). The main structural component of the capsid is VP2, which accounts for about 95% of the total protein in the infectious virus [11]. Despite its low concentration in the virion, the unique region (VP1u) is a dominant epitope target for neutralizing antibodies and has phospholipase A2 activity, which is necessary for B19 infectivity [12]. Growing evidence shows that this enzymatic activity plays a central role in the induction of autoimmune and inflammatory processes.

The main nonstructural protein of PV-B19 is NS1 (74 kD) coded by the left side (5′ end) of the genome, while VP1 and VP2 are coded on the right side (3′ end) (Fig. 14.1). The NS1 has multiple functions, such as transactivation of the viral p6 promoter and helicase activity, both necessary for viral replication. Furthermore, NS1 is involved in triggering the apoptosis of erythroid lineage during B19 infection [13], and is able to transactivate other cellular genes such as IL-6 and TNF-α, and induce the activation of the signal transducer STAT3 [14–16]. The clinical value of these findings is still unknown. There are two additional proteins, 11 kDa and 7.5 kDa, whose functions have not been established yet.

In 1993, the PV-B19 receptor was described. Brown et al. demonstrated that B19 binds to the antigen of the blood-group P system or globoside, measured by hemagglutination and that erythrocytes lacking P antigen were not agglutinated [9, 17]. They were also able to block the viral binding with purified globoside or monoclonal antibody against globoside.

The P antigen is mainly found in erythrocytes, erythroblasts, megakaryocytes, endothelial cells, liver and heart cells. However, Cooling et al. described it also in synovial tissue [18]. Later, α5β1 integrin and Ku80 have been described as co-receptors for PV-B19, but their function has not been elucidated yet [19, 20].

PV-B19 has high tropism for human erythroid progenitor cells; however, its replication in vitro is restricted to few permissive cell lines, such as megakaryoblastoid cell lines

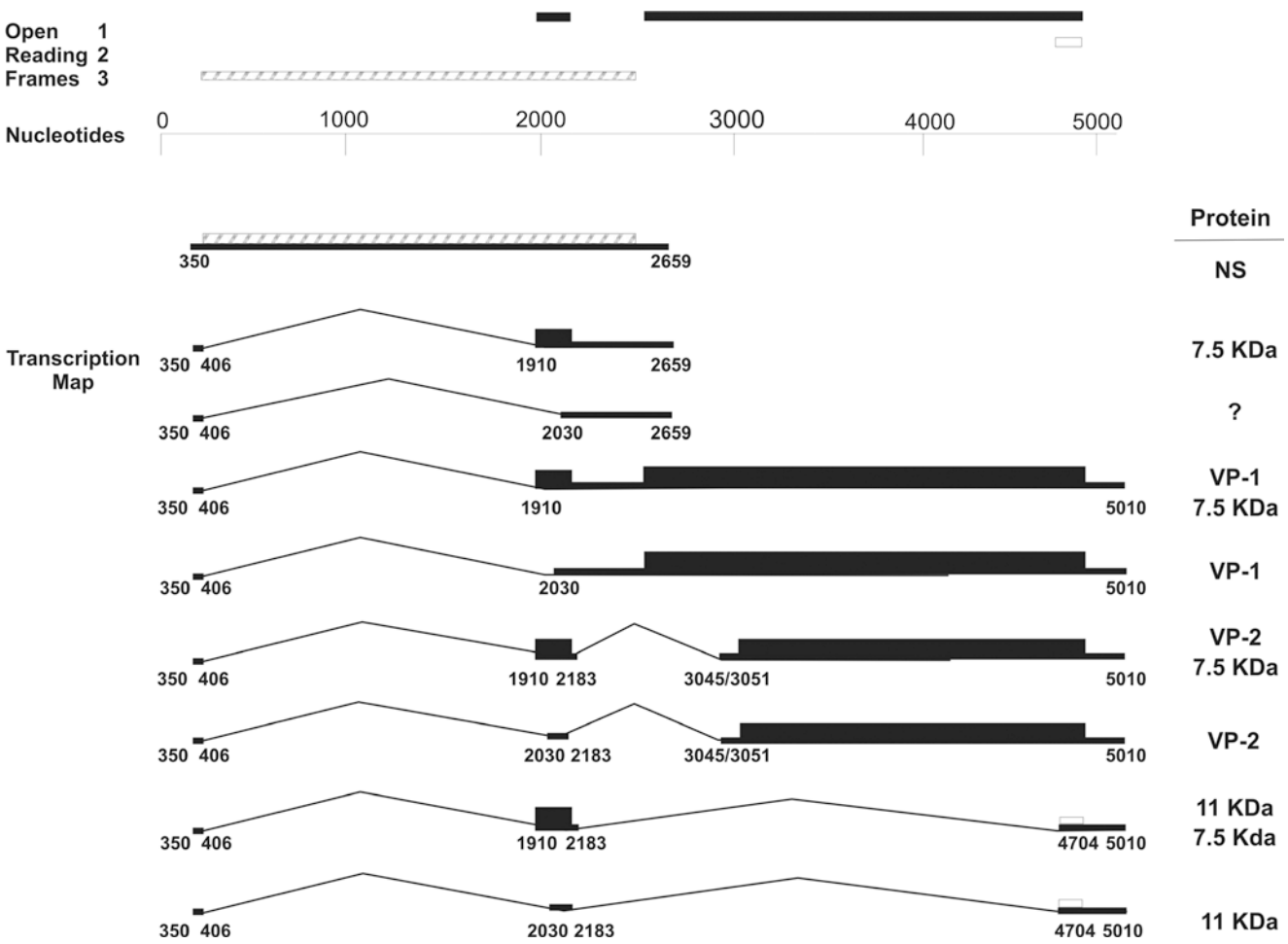

Fig. 14.1 Parvovirus B19-Transcription Map

(UT7 and MB-02) and erythroleukemia cell lines (JK-1 and KU812Ep6). Ex vivo-generated pure population of CD36 cells – with high expression of globoside – shows better permissivity than the former [21].

B19 genotypes were long unknown. Strains with genomic variations greater than expected, such as V9, were first described by late 1990s, strains with genomic variations greater than expected, such as V9, were first described. Currently, at least 3 genotypes with different distribution frequency have been accepted after analyzing groups of different ages and geographic region [22].

Until recently, PV-B19 was the only parvovirus known to produce disease in humans. Other parvoviruses have been identified on the last decade, including human bocavirus 1–4 (HBoV), parvovirus 4 (PARV4), and human bufavirus. Most of them are emerging viruses whose human diseases are of unclear significance yet.

PARV4 was isolated in blood samples from individuals with acute infections of undiagnosed etiology, in pooled plasma or plasma-derived blood products, and in individuals co-infected with HCV and HIV [23]. Unlike PV-B19, whose main transmission route is respiratory PARV4 seems to be transmitted by parenteral route according to those risk groups. Three PARV4 genotypes have been described, but its role in human disease is yet unknown.

Human Bocavirus 1 (HBoV1), was identified in pooled respiratory samples and subsequently found to be distributed worldwide among children under 5 years. It affects both upper and lower respiratory tract, sometimes as a co-infection with another virus [24]. It has been reported to cause pneumonia, bronchiolitis, acute otitis media, asthma exacerbations, and life-threatening respiratory failure [10]. Clinical and epidemiological data suggest an air route or direct contact transmission. A more extensive description of this virus is beyond the scope of this chapter.

To date, no cross-reactions of HBoV, PARV4, and B19-specific humoral responses have been described.

Pathogenesis

Most of the knowledge on the pathogenesis of PV-B19 infection comes from epidemiologic studies and experimental infection of healthy volunteers. In 1985, Anderson et al. inoculated intranasally normal volunteers with human parvovirus obtained from an asymptomatic blood donor [25]. They demonstrated that B19 replicates initially in the mucosa and that viremia starts on day 6 after inoculation, reaches its peak on days 8–9, and persists for about a week. They also showed that volunteers with previous IgG anti-PV-B19 did not develop viremia. During the second week after inoculation patients developed high IgM titers that persisted about 3 months, and at the end of the second week, IgG anti-PV-B19 appeared and where life lasting (Fig. 14.2).

Symptoms associated with this experimental trial resemble the natural infection and show a bimodal manifestation. A febrile flu-like syndrome with malaise and myalgias appeared during the viremia in some patients, and at the end of the second week after inoculation, when IgG appears and the viremia resolves, rash and arthralgias developed in some patients. This latter phase could persist for around 7–10 days. Associated with these symptoms, areticulocytosis develops during weeks 2 and 3 after infection and can persist during week 4. This is due to viral tropism for erythrocyte lines. There can be a subtle drop in hemoglobin following the period of areticulocytosis. Neutropenia and lymphopenia may appear on week 2 and 3. Although platelets usually remain within the normal range, a slight decrease could be found. All these hematologic alterations resolve spontaneously at week 4.

Alternatively, immune-compromised patients present a longer viremic phase, as they do not develop a normal serologic response [26]. On the other hand, in patients with high bone marrow turnover, like patients with hemolytic anemia, the hematopoietic arrest induced by the virus is able to produce profound anemia, sometimes accompanied by thrombocytopenia and leucopenia [26].

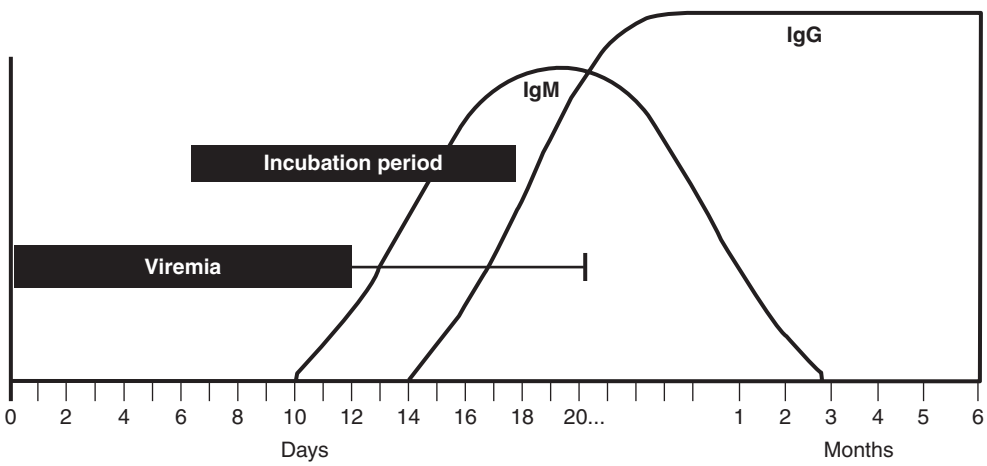

Fig. 14.2 Pathogenesis of Parvovirus B19 Infection

In normal conditions, the incubation period for this air transmitted virus lasts between 6 and 18 days. Other routes are blood derivates, vertically during pregnancy and during bone marrow or solid organ transplantation [27].

Epidemiology

The human is the only known reservoir of this worldwide virus. Infection is mainly acquired during outbreaks in winter and spring that used to occur every 3–4 years. Usually, the infection is acquired during these outbreaks by children attending daycare or elementary schools. These infected children carried the virus to their home were non-previously infected parents and siblings can acquire the infection. Nevertheless, sporadic cases of this illness have also been described. The seroprevalence of specific IgG ranges between 2–21% in children and 40–60% in adults.

Dermatologic Involvement

Parvovirus B19 infection can induce a myriad of cutaneous manifestations. While erythema infectiosum is the most frequent presentation in children, adults sometimes present with papular-purpuric gloves and socks syndrome [28, 29]. Many other cutaneous patterns have been described but they are mainly anecdotal [30]. Scattered cases have been published associating PV-B19 and generalized vanishing livedo reticularis [31], erythema multiforme [32], vesico-pustular skin eruption [33], Schönlein–Henoch purpura [34], thrombotic thrombocytopenic purpura [35], idiopathic thrombocytopenic purpura [36], and on a histopathologic study, eruptions compatible with cutaneous lupus, dermatomyositis, and Sweet's syndrome [37]. A common histological pattern was described, regardless of the clinical presentation, showing an interstitial histiocytic infiltrate plus lymphocytic interface dermatitis or mononuclear cell vascular reaction [37].

Erythema Infectiosum

Erythema infectiosum (EI), also known as fifth disease, is the classical cutaneous manifestation of the disease. It is a mild, acute, exanthematous disease that occurs mostly in children, but it also affects 44% of the infected adults [38]. It usually preceded by fever and systemic symptoms, and the rash appears after the defervescence of the fever [39].

Cutaneous involvement of EI presents in three phases [40, 41]:

The first stage is a malar exanthema that appears suddenly, described as "slapped cheek," and it usually lasts 1–4 days. This rash is nonpruritic and turns more intense when exposed to heat or sunlight. Perioral area is spared, giving a pallor appearance. Simultaneously, a dark red enanthem may appear on the palate. This stage is more frequently seen in children than in adults [42].

The second stage begins 1 day after the appearance of malar rash and consists of a maculopapular eruption on the trunk and extremities that it is seldom pruritic. The macules then turn confluent and present central blanching, giving a reticulated aspect, and later disappear without scars. This whole stage lasts for 5 days [40]. This is the most characteristic stage, with its lacelike appearance that is almost pathognomonic [43].

The last stage has an average duration of 1–4 weeks, and it is characterized by the recrudescence of the exanthema induced by emotional stress, heat, and sunlight exposure [6, 40].

Papular-Purpuric Gloves and Socks Syndrome

Papular-purpuric gloves and socks syndrome (PPGSS) was first described as an entity in 1990 by Harms et al. [44], and then related to PV-B19 by Bagot et al. in 1991 [45]. Nevertheless, this pattern is not pathognomonic [46] since it has also been associated with CMV, Coxsackie B6, measles, EBV, HHV-6, and drugs [47]. In all cases, it is believed to be due to a cytotoxic reaction against skin cells – endothelial and epidermal – expressing viral antigens [48].

It is described to affect mainly young adults without gender predilection, especially during spring and summer [49], and to resolve spontaneously after 7–14 days in a non-scaring fashion [28, 50]. Fever and constitutional symptoms might accompany the eruption.

Cutaneous manifestations begin with edema and erythema distributed symmetrically in hands and feet with sharp demarcation [30], with gloves and socks shape. Later, millimeter erythematous papular-purpuric lesions appear, accompanied by pruritus or pain. These lesions may be isolated or confluent [49]. It may later add papular exanthema on elbows, knees, trunk, buttocks, and thighs [44].

Oral manifestations are present in over 50% of the affected patients. Oral lesions might range from multiple petechiae in the palate to enanthem, vesicles, pustules or small, shallow and usually painful ulcerations in the mucosa and soft and hard palate. Lips may present swelling, aphthae, and angular cheilitis. Pharynx may be involved too [51]. And although infrequent, genital mucosa can be affected in the same way [52].

Arthropathy and Rheumatological Features

The association between erythema infectiosum and arthritis was described as early as 1966 in an article of the NEJM, even before the discovery of Parvovirus B19 as the subjacent

etiological agent [2]. And although our knowledge on this clinical feature has increased since then, there is still debate on the potential of the infection to induce autoimmunity and its eventual role on the development of diseases such as rheumatoid arthritis.

Parvovirus B19 infection is the causative agent for 3.3% of the acute reactive arthritis [53]. It induces joint symptoms on 8% of the infected children, usually preceded by erythema infectiosum, and up to 80% of infected adults, where it is often the only manifestation. Arthritis is more frequent in women (59%) than in men (30%) [54]. Adults and children also differ on the phenotype of the joint involvement. Adults' phenotype often resembles rheumatoid arthritis, with acute, symmetric, polyarticular involvement, predominantly of proximal interphalangeal and metacarpophalangeal joints (75%), knees (65%), wrists (55%), and ankles (40%) [55]. Children instead tend to show an asymmetric and pauciarticular involvement, most often affecting knees (82%) and only occasionally hands and feet (5%), that resembles of pauciarticular juvenile arthritis [56]. Joint symptoms usually last for 1–3 weeks, but 20% of the affected patients evolve to chronic arthritis [57] that is nonerosive [58].

Parvovirus related arthritis can be difficult to distinguish from early onset rheumatoid arthritis since it affects mainly middle-aged women and presents with symmetrical polyarticular small joints involvement. Laboratory testing might show an elevation of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). Although auto-antibodies can be positive, especially antinuclear antibodies and rheumatoid factor, these findings are usually transient [59]. There are controversial data regarding a possible etiological role of Parvovirus B19 in chronic inflammatory conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Evidence Favoring an Association

There is broad consensus on the role of different infectious agents as triggers of RA, such as Porphyromonas Gingivalis, Proteus Mirabilis, and to a lesser extent, mycoplasma, Epstein–Barr virus, and cytomegalovirus [60]. Parvovirus B19 might as well act in the same way.

In 1999, Altschuler published a very interesting historical observation in The Lancet. While the first reports and archeological findings of RA in Europe date back to the fifteenth century, there is evidence of its presence in America for thousands of years. Coincidently, Parvovirus B19 is considered as a "new world" virus, with the first clinical description compatible with erythema infectiosum in Europe made at the end of the nineteenth century [61]. Although this does not provide any causal evidence, it makes us wonder if this is just fortuity. Nevertheless, we should keep in mind that other risk factors for RA, such as tobacco, were also introduced from the New World [62].

A study by Takahashi et al. found viral DNA in leukocytes and other peripheral blood cells, and in the synovium cells of RA patients more frequently than on osteoarthritis patients [63]. Another publication found a higher prevalence of viral DNA in cell-free blood plasma – meaning persistent infection on active phase – in RA patients compared to matched healthy patients, and hypothesized that this is due to impaired production of neutralizing antiVP1u antibodies [60]. Additionally, a publication by Takahashi found an enhanced production of IL-6 and TNF-α in synovium cells of RA patients infected with PV-B19 [63], providing a proinflammatory environment. And finally, Kakurina et al. found a correlation between RA activity and active B19 infection [64]. There are several hypotheses looking for biological plausibility for this association, including chronic viremia [65] and cytotoxic effects of NS1 protein [66], presence of P globoside antigen in the synovium [67] genetic background, cytokine phenotype, immune mimicry [68], immune-complex deposition, and immunity impairment [53].

Studies on genetics found that HLA-DRB1∗01, ∗04 and ∗07, HLA-B27, B35, and B49 are associated with symptomatic infection, while HLA-DR4 is associated with the severity of symptoms and chronicity. Noteworthy, shared epitope, once thought to be the link between genes and symptoms, cannot fully explain clinical manifestations since only HLA-DRB1∗01 and ∗04 carry the sequence but the rest of the alleles do not [65, 69].

Cytokine genotyping presents conflicting results. While some publications found increased production of inflammatory cytokines that may explain clinical manifestations, other studies described an overexpression of immune-inhibitory cytokines, thought to lead to enhanced viral expression and persistence of viremia.

Kerr et al. found that sera from patients with acute B19 infection have raised levels of TNF-α, INF-γ and IL-6 that can persist for several years [70]. Moreover, experimental studies on synovial fibroblasts from Parvovirus B19 positive RA patients showed an increased production of TNF-α and IL-6 [63], and that normal synovial fibroblast cultured with Parvovirus B19 switched into an invasive phenotype [67]. This can be explained by another study that described that the VP1u protein from the PV-B19 capsid has a secreted phospholipase A_2 ($sPLA_2$) motif that hydrolyzes membrane lipids and releases arachidonic acid. This enhances the production of prostaglandins by the cyclooxygenase, initiating the inflammatory cascade [71].

Surprisingly, another study from Kerr et al. found a reduced level of TNF-α, IL-6, INF-γ, and TGF-β1 in patients with B19 related arthritis and lower TGF-β1 level in patients with rash at acute B19 infection [70, 72]. And concordantly,

a study on a group of patients with symptomatic infection showed a low frequency of TNF-α-308 A allele – a high TNF production phenotype – that can lead to insufficient production of TNF. Similarly, the TGF-β1 + 869 T allele, a variant of the immune inhibitory TGF-β1 with high transcriptional activity, was also associated with symptomatic disease [73]. Other studies found an increased level of the anti-inflammatory cytokine IL-4 [74].

Evidence Against the Association

On the other hand, there are studies that found that the seroprevalence of PV-B19 in RA patients is not higher than in patients with osteoarthritis (OA) and that this is also true for the presence of viral DNA in the synovium [75]. A study on healthy patients that underwent arthroscopy after trauma showed that 67% of the patients with past PV-B19 infection were positive for viral DNA in synoviocytes [76]. Another publication found no difference in the presence of viral DNA in serum from RA patients and controls [77]. Finally, a study on RA discordant twins, either monozygotic or dizygotic, found no augmented risk regarding PV-B19 previous exposure [78].

Other Suspected Clinical Associations with PV-B19

Besides RA, many other publications found higher seroprevalence of PV-B19 in patients with juvenile rheumatoid arthritis, SLE, Sjögren's Syndrome and chronic fatigue syndrome than in controls [60]. In 1992, Cope et al. published the first description of a patient with a diagnosis of SLE after parvoviral infection [79]. Following that study, several case reports and series suggested an association between PV-B19 and SLE [80], but no studies with a strong level of evidence were published.

There is a debate on the seropositivity rate of PV-B19 in SLE patients compared to controls. While Bengtsson et al. state that the seroprevalence is not increased in SLE patients [81], Pugliese et al. state the opposite [82]. Additionally, prospective studies failed to describe an association between SLE and PV-B19 [83]. Moreover, Parvovirus B19 can be easily misdiagnosed as SLE [84] since it can induce autoantibodies production, and can clinically manifest with fever, arthritis, arthralgia, rash, lymphadenitis, and even anecdotal cases of hemolytic anemia [85] and glomerulonephritis [86]. In contrast with SLE, PV-B19 is a self-limited disease, and symptoms are usually transient.

Regarding antiphospholipid syndrome, a recent meta-analysis found an eight-fold increase in the risk of developing elevated anticardiolipin antibodies but no higher risk for thrombosis. Pregnancy losses had a trend to be higher, but this was not statistically significant and it can be explained by the inherent increased obstetrical risk of the virus. This study did not show an increased risk for lupus anticoagulant nor immunoglobulins anti β2 glycoprotein I [87]. It is hypothesized that the phospholipase A2 of the VP1 might trigger the production of antiphospholipid antibodies [88]. The specificity of antiphospholipid antibodies in patients with acute parvovirus infection resemble those found in SLE, that are able to bind to negatively charged phospholipids and cardiolipin, in a cofactors dependence pathway, and differ from those found in other viral or lues infections that react only to the phospholipids [89].

PV-B19 has also been linked to juvenile idiopathic arthritis (JIA), although there are conflicting opinions on this subject [90–92] and misdiagnosis can be especially frequent among these patients since they share epidemiology – school-age children – and clinical aspects such as fever, rash, and asymmetrical oligoarthritis. Oğus et al. performed a prospective case-control study that found a significant difference for IgM's seropositivity for PV-B19 in patients seen for arthropathy vs. patients seen for other reasons. And among those patients followed for arthropathy, the IgM PV-B19 group showed a higher progress rate towards JIA [93]. Later, Gonzalez et al. found a persistent B19 infection in 48% of the JIA patients vs. 0% on controls, and this was especially true on children with active JIA [94]. Despite this, this data is not strong enough to suggest an association.

Several reports have been published on PV-B19 and different type of vasculitis, including small, medium and large-sized vessel. Most of them are case reports that provide low-grade evidence [34, 95–98]. The best evidence comes from a study on 50 consecutive patients undergoing a temporal artery biopsy, where histologic evidence of giant cell arteritis was significantly associated with the presence of viral DNA [99], and later supported by further studies [100]. Conversely, Eden et al. found no increased seroprevalence of PV-B19 on patients with ANCA associated vasculitis [101], and studies such as Yoto's showed no peak of incidence of Kawasaki after an outbreak of PV-B19 [102], as could have been expected in case of a causal relationship.

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) have also been associated with PV-B19. The first description is a case series in which FM's onset coincides with PV-B19 infection [103]. This adds to a publication in 1987 that states that fibromyalgia appears in 55% of the patients after a "flu-like" disease [104]. And although there are some publications supporting this theory both for CFS [105] and FM [106], many other publications stand against it [107–109]. Additionally, anecdotal reports of PV-B19 in Still's Disease [110], inflammasome activation [111], uveitis [112, 113], systemic sclerosis [114, 115], and myositis [116, 117] have been described.

In conclusion, current data is not strong enough to state Parvovirus B19 as a causative agent for RA nor any other rheumatic disease, and PV-B19 certainly does not fulfill the Bradford Hill Criteria [118, 119] for causality in any of them. Since it is a ubiquitous virus, the coexistence of PV-B19 and the presentation of a disease might be mere coincidence. And the fact that so many different diseases – with different underlying pathogenic mechanisms – claim for an association, reinforces this opinion. Nevertheless, PV-B19 might act as a trigger in genetically predisposed patients [75], and several publications found an association between persistence of viremia and activity of different diseases.

Hematological Manifestations

In 1981, Pattison et al. performed a study on Transient Aplastic Crisis (TAC) in children with sickle cell anemia and found the first association of Parvovirus B19 and a clinical manifestation [4]. Ever since, our knowledge on the subject has been increasing.

As it was previously mentioned, Parvovirus B19 is highly tropic for bone marrow since it replicates in the erythroid progenitor cells, on which it has a cytotoxic effect. This process can induce different clinical consequences depending on the immunological and hematological status of the host [120].

Studies on healthy volunteers showed a sudden stop on red cell production between the eighth and seventeenth day of infection that resolves when viremia is over. This led to the absence of reticulocytes in peripheral blood and a drop in hemoglobin levels, followed by the restitution of levels previous to inoculation on day 26 [25]. In contrast, individuals with hemolytic disorders suffer from TAC, and immunocompromised patients, in response to persistent viremia, might develop chronic anemia and pure red cell aplasia (PRCA) [121].

Transient Aplastic Crisis is a transitory anemic state resulting of an impaired ability to produce red cells – in this case, due to parvoviral infection – in patients with a wide range of hemolytic disorders that rely on increased hematopoiesis. This includes, among others, hereditary spherocytosis, thalassemia, red cells enzymopathies, autoimmune hemolytic anemia, as well as erythroid stress such as hemorrhage or iron deficiency [121]. Despite there are several reports of aplastic crisis due to other pathogens, PV-B19 is the main etiological agent of community-acquired aplastic crisis [122].

On the other hand, PRCA is the result of persistent PV-B19 replication due to an impaired immunity that fails in mounting an adequate immune response. The result is persistent normocytic normochromic anemia with reticulocytopenia and marked reduction of bone marrow precursors [123]. PRCA secondary to persistent PV-B19 infection was described in patients with congenital immunodeficiency syndromes, acquired immunodeficiency syndromes such as AIDS, and iatrogenically immunosuppressed patients such as oncological patients, transplant hosts or any patient with immunosuppressive drugs [120].

PV-B19 has also been associated with the hemophagocytic syndrome, both in children and adults, and on immunocompetent and immunocompromised patients. In these cases, the hemophagocytic syndrome was usually benign and self-limiting [121].

Another hematological manifestation of the infection, although rare, is hepatitis-associated aplastic anemia, defined as bone marrow failure following acute hepatic injury through immunologic mechanisms, including hemophagocytic syndrome [124]. This is a life-threatening condition that, when untreated, progresses rapidly and has a fatality rate of 78–88% and mean survival time of 2 months. However, first-line treatment is hematopoietic stem cells transplantation, with a response rate of 82%, and immunosuppressive therapy with cyclosporine and anti-thymeglobulin with a response rate of 70% [125]. Additionally, there are reports on autoimmune neutropenia [25] autoimmune thrombocytopenia [36] and autoimmune hemolytic anemia [126].

Kidney Involvement

Although it is not a common feature, Parvovirus B19 infection has been associated with several renal manifestations. Among them are acute post-infectious glomerulonephritis [127, 128], Schönlein-Henoch purpura nephritis [34], thrombotic microangiopathy [129], and collapsing glomerulopathy [130]. Post-infectious acute glomerulonephritis has female preponderance, tends to affect patients on the second or third decade, and usually shows mild proteinuria and a self-limited course, with studies showing a high frequency of spontaneous remission [128, 131, 132].

Collapsing glomerulopathy is a severe form of glomerulopathy, characterized by segmental or global collapse of the glomerular capillaries, hypertrophy, and hyperplasia of the epithelial cells and severe tubulointerstitial inflammation [127]. It is clinically manifested with heavy proteinuria, poor response to therapy [133] and prognosis [134]. The hypothesized underlying mechanism for collapsing glomerulopathy is viral direct toxicity on the podocytes, regarding that it bears P globoside antigen, and especially on a risk population homozygous for APOL1 alleles recently described [132, 134]. Nevertheless, actual evidence is still not strong enough to show a causative relationship between PV-B19 and kidney involvement [135].

Liver Involvement

Parvovirus B19 induced hepatitis is a rare presentation that occurs on 4.1% of patients infected [136], and clinically ranges from a mild elevation of transaminases to fulminant liver failure, or even chronic hepatitis [137]. Acute hepatitis is more frequent and severe on the pediatric population, although it can affect both children and adults regardless of their immunological status. Prognosis is usually good, with spontaneous remission, and cases of fulminant hepatitis are rare [137]. The proposed treatment for fulminant hepatitis consists of IVIG and steroid infusion and injections of granulocyte colony stimulating factor for 3 months [137].

Parvovirus B19 is also suggested as an etiological agent for hepatitis-associated aplastic anemia (HAAA) [138], a variant of acquired aplastic anemia, in which acute hepatitis leads to marrow failure and pancytopenia. It is a disease with poor prognosis and treatments range from antithymocyte globulin, cyclosporine, and cyclophosphamide to hematopoietic stem cell transplantation [139].

Reports on chronic hepatitis are conflicting [140]. While Toan et al. affirm that the coinfection Hepatitis B Virus/PV-B19 has a higher probability of developing more severe hepatitis [141], studies by Hsu et al. and by Wang et al. found that the persistence of PV-B19 does not correlate with worsening of liver function in patients with chronic Hepatitis B and Hepatitis C [142, 143]. Hepatic damage is thought to be due to viral direct cytopathic effect and immunological imbalance due to an elevation of INF-γ, TNF-α, and IL-2[137].

Myocardial Involvement

Parvovirus B19 has been associated with acute myocarditis, chronic myocarditis, dilated myocardiopathy, and myocardial infarction [144]. Nevertheless, the evidence is conflicting and there is still debate on if PV-B19 is a simple bystander or if it plays an etiological role in myocarditis.

Myocarditis is usually described in three phases: First, myocardiocyte destruction by virus-mediated lysis; second, inflammatory response to the previous destruction; and last, fibrosis [145]. Clinical spectrum may range from complete recovery (50%), ventricular arrhythmias, fulminant myocarditis, or long term evolution to dilated myocardiopathy [145].

The diagnostic gold standard for myocarditis is endomyocardial biopsy fulfilling histological Dallas criteria, together with immunochemistry and viral PCR [145]. But the significance of parvoviral DNA presence in myocardial biopsies is controversial since it can be found in healthy patients' hearts [146].

Since P globoside is only present on fetal myocardiocytes and post-partum myocardiocytes that are non-replicative, cytotoxic viral replication is unlikely as the pathogenic mechanism. On the other hand, PV-B19 has been detected on endothelial cells by in-situ hybridization, and thereafter, the proposed mechanism for myocardial damage is necrosis and inflammation due to endothelial dysfunction and enhanced inflammatory cytokines production [147, 148].

The proposed treatment for myocarditis is based on supportive care with beta-blockers and angiotensin-converting enzyme-inhibitors. Use of immunosuppressant drugs might be considered in patients with biopsies showing active inflammation [145]. Use of IVIG might be considered based on a study that shows cardiac improvement and PV-B19 eradication with its use in patients with chronic cardiomyopathy and high parvoviral load [149]. Definite evidence will be provided by a recently finished but not yet published placebo-controlled trial (clinicaltrials.gov Identifier: NCT00892112) on the efficacy of high dose IVIG for chronic PV-B19 cardiomyopathy.

Neurological Involvement

Neurological involvement in PV-B19 infection is of relevance since manifestations may be serious and leave sequela. These manifestations are unusual, and consequently, most of the evidence is provided by case reports.

Parvovirus infection has been associated with Central Nervous System (CNS) and Peripheral Nervous System (PNS) manifestations. The most reported CNS manifestations are encephalopathy, encephalitis, meningitis, stroke, seizures, chorea, and cerebellar ataxia, while PNS is characterized by cranial and peripheral neuropathies, especially brachial plexus neuropathy, and Guillain–Barre syndrome [150].

CNS manifestations are more frequently seen in children, while PNS involvement is usually seen in adults. Immunocompromised patients do not show different phenotypes of disease nor different prognosis [150]. Interestingly, immunocompetent patients only differ from immunocompromised in the higher presence of accompanying viral symptoms such as rash and arthralgia.

Central Nervous System Manifestations

Encephalopathy: Encephalopathy is the most common neurological manifestation of PV-B19, accounting for 38% of the total [151]. The most frequent manifestations are altered mental status and seizures, usually generalized, and

focal neurological signs [150, 151]. When present, erythema infectiosum tends to appear simultaneously with neurological symptoms [152]. Sequelae, such as epilepsy and cognitive deficit, are reported on 33% of affected patients. The death rate is reported to be 9% [151].

Meningitis: Parvovirus infection presents as aseptic meningitis with fever, neck stiffness, vomiting and headache [150]. Patients usually present full recovery [152].

Stroke: Stroke accounts for 13% of CNS manifestations. A retrospective case-control study on children with stroke found a prevalence of 6% of PV-B19 in the stroke group and none in controls [153]. Other publications described stroke mainly on patients with sickle cell anemia during aplastic crisis [154] and immunocompromised children with PRCA [150]. Sequelae are as frequent as in other causes of stroke [150].

CNS Vasculitis: There is only one report on recurrent CNS vasculitis in a child with persistent PV-B19 infection that resolved with IVIG when viremia was solved [155].

Proposed mechanisms for neurological involvement are direct viral toxicity, dysregulated cytokine production and immune-complex deposition on vessel walls, that induce production of lysozymes with the consequential vessel destruction, hemorrhage, and necrosis [152, 156].

Peripheral Nervous System

Brachial Plexus Neuropathy: Also known as neuralgic amyotrophy, it is the most common peripheral neuropathy. It is an axonal disorder characterized by sudden onset of pain and paresthesia of the shoulder and arm, followed by weakness of periscapular and arm muscles [152]. Electromyography shows denervation and slow conduction velocity of the nerve [150]. Symptoms usually last 2–6 months, but there are reports of symptoms lasting up to 3 years [150].

Guillain–Barre Syndrome: There are several reports on classical Guillain–Barre syndrome triggered by PV-B19. All cases are resolved, either using IVIG or plasma exchange [144]. Although available evidence is weak, the use of IVIG is recommended for severe cases [152]. According to a systematic review, only half of the patients treated with IVIG or high dose of steroids showed improvement, but 44% of patients that did not receive treatment presented sequela or died while none of the treated patients did. There are cases describing the failure to IVIG that responded to steroids and vice versa [150].

Obstetric Complications

Parvovirus B19 is a serious concern during pregnancy since it is a member of the TORCH group – a group of infections known as major contributors to prenatal, perinatal, and postnatal morbidity and mortality [157]. Obstetric complications may appear as the result of fetal infection with PV-B19 through vertical transmission of a susceptible pregnant woman. Vertical transmission's risk is about 33% in a viremic gravid woman, being higher during the first and second trimester and lower in the third [158].

A large study by Valeur-Jensen published in 1999 found evidence of past PV-B19 infection in 65% of pregnant women in Denmark, and a seroconversion rate among susceptible women of 1.5% during endemic periods and 13% during epidemics. And remarkably, the main source of the virus was each woman's own children [159]. Maternal infection is diagnosed by the detection of PV-B19 specific IgM antibodies, and should only be studied on women exposed to PV-B19, or presenting clinical manifestations suggestive of the disease (erythema infectiosum or arthritis), or as part of the workup in cases of fetal hydrops or intrauterine fetal death [160]. Clinical manifestations for the child-bearing woman and disease severity of PV-B19 infection do not differ from those observed in healthy, non-pregnant women [161].

In the case of documented maternal infection, diagnostic procedures on the fetus are only performed when obstetric complications are suspected (fetal anemia, Hydrops Fetalis). Diagnosis of fetal infection relies on the detection of PV-B19 DNA in amniotic fluid or cord blood [161], since the immaturity of the fetal immune system does not warrant an appropriate immunoglobulin response [162]. Umbilical cord puncture may be risky since thrombocytopenia is present in almost half of the infected fetus, and severe thrombocytopenia can lead to fetal death due to bleeding [163].

Although most fetal infections have spontaneous resolution without adverse outcomes [164], obstetric complications are serious and might range from fetal anemia to non-immune hydrops fetalis, and stillbirth. The risk of fetal loss is estimated at 13% during the first half of the pregnancy, and 0.5% in the second half [165]. Fetal deaths during the first 16 weeks are usually due to severe anemia, while Non-Immune Hydrops Fetalis (NIHF) accounts for most of the deaths in the second half of pregnancy [166].

Parvovirus B19 fetal infection is possible since P-antigen is present on the trophoblast layer of the placenta, allowing vertical transmission. This is especially true during the first trimester of pregnancy when the receptor is widely expressed, and then its expression diminishes gradually until disappearing in the third trimester [167]. After reaching fetal circulation, PV-B19 infects all the P-Antigen bearing cells, including both erythroid cells and non-erythroid cells such as megakaryocytes, fibroblasts, endothelial cells, and cardiac myocytes [168].

During the first 2 trimesters of gestation, hematopoiesis is located at the liver and its very active since the erythrocyte cell mass is constantly increasing and fetal red blood cells lifespan is about 45–70 days [169]. Both factors make the fetus very vulnerable to any pause in the hematopoietic production, and consequently, prone to fetal anemia.

On the other hand, NIHF is one of the most serious obstetric complications of parvoviral infection. The overall incidence of NIHF in women infected during pregnancy is 2.9% [160], being 4.7% during the first half of the gestation and 2.3% in the second half. The interval between maternal infection and diagnosis of NIHF ranges between 1 and 20 weeks, with a median interval of 3 weeks [162]. Non-immune hydrops fetalis does not usually develop until an absolute hemoglobin level below 7 gr/L [170]. Hydrops is caused by a high output cardiac failure due to hypoxia and anemia, combined with viral myocarditis and impaired hepatic function due to direct and indirect hepatocyte damage [160].

Additionally, there are reports on organ-specific fetal complications, including gastrointestinal injuries (hyperechogenic bowel and meconium peritonitis), ocular injuries (corneal opacification and ocular malformations), myocardiopathy, and brain lesions (hydrocephalus, cerebellar hemorrhage, polymicrogyria, neurodevelopment delay, and cerebral palsy) [160, 162, 169]. Brain lesions are thought to be caused by hydrops [171].

Treatment is based on intrauterine transfusion (IUT) with fresh, irradiated, type 0 RH negative and cross-matched to a maternal sample red blood cells, to prevent graft vs. host reactions, packed to a hematocrit of 80% to avoid fetal overload [172]. Although expectant management may be appropriate in cases of mild or improving anemia, assessed by ultrasound [173], Fairley et al. found a seven-fold reduction of fetal death in IUT patients vs. expectant management [174]. Thrombocytopenia should be considered while performing IUT, since it is a common finding (40% of fetal HP-B19 infections), and it is associated with procedure-related fetal loss. Intravenous immunoglobulin might be useful in selected cases, such as virus-induced severe pre-eclampsia [175] and immunodeficient patients [176]. Additionally, there are published cases on placental exchange transfusion [177] and PV-B19-specific immunoglobulin therapy in the fetal peritoneal cavity [178].

Overall, a recent meta-analysis on fetal outcome found a death risk (including intrauterine and neonatal death) of 29% in the hydropic fetus and 4.4% in non-hydropic. Spontaneous resolution occurred in 5.2% of the hydropic fetus and 49.6% of non-hydropic, while intrauterine transfusions resolved the infection in 55% of the hydropic fetus and 100% of non-hydropic [171].

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Human Immunodeficiency Virus Infection: Spectrum of Rheumatic Manifestations

15

Luis E. Vega and Luis R. Espinoza

Introduction

Despite extraordinary advances in diagnostics, therapeutics, and vaccine development, emerging and reemerging viral diseases have occurred during the past several decades [1, 2]. Several factors that contributed to the emergence of recent epidemics have been identified including those related to the microbial agent, the human host, and the human environment. Also among the most important factors are genetic adaptations of the microbial agent, international travel, human susceptibility to infection, population growth, an aging population, climate and weather changes, and expanding vector habitats [2–5]. Three recent examples of disease emergence are the Middle East Respiratory syndrome coronavirus (MERS-CoV), Chikungunya, and the Zika viruses, which represent new viral entities or viruses emergent in new geographic locales and characterized by novel complications [6, 7]. However, the most important newest example of an emergent infectious disease is human immunodeficiency virus (HIV) infection, which emerged a century ago in a primate host(s), and subsequently spread within the human population. HIV-related acquired immune deficiency syndrome (AIDS), the most dreadful complication, was first recognized in 1981 in men who have sex with men, injection drug users, and recipients of blood transfusions [8–10]. Subsequently, in the year 1983, Francois Barré-Sinoussi, Luc Montagnier, and others from the Institute Pasteur in Paris identified the etiologic agent of this disease and called it the human immunodeficiency virus (HIV). Both French virologists were awarded the Nobel Prize in 2008 for this discovery. At present, however, HIV infection has become a global disease affecting heterosexual individuals, especially within the developing world [11].

Table 15.1 Differences between HIV 1 and HIV 2

Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Chimpanzee
HIV-2	Low	Low	West Africa	Sooty Mangabey

The virus HIV belongs to the Retroviridae family and genus lentivirus. There are two serotypes: HIV 1 and HIV 2. HIV1 is the etiologic agent of epidemic AIDS. See some differences between both serotypes (Table 15.1).

Structure

HIV has a lipid envelope, in which two glycoproteins (gp), the gp41 and gp120, are inserted. These two viral glycoproteins are responsible for attachment to the host cell. Beneath the envelope, is the matrix p17, the core proteins p24 and p6 and the nucleocapsid protein p7. Within the viral core lie two copies of the viral ribonucleic acid (RNA) genome, together with the protease, integrase, and reverse transcriptase enzymes (Fig. 15.1). All of these structures are codified by different viral genes.

Life Cycle

Once the human immunodeficiency virus enters in the body of a human being, it binds to its specific receptor. The HIV virus attaches to the CD4 receptor which is present on the surface of the CD4+ T cell and then either a CCR5 or CXCR4 co-receptor, to replicate itself and infect other cells. After binding to the CD4+ receptor the virus uses the machinery of the CD4+ T cell, to replicate and spread throughout the body. The process of replication is carried out in several stages: binding, fusion, reverse transcription, integration, replication, assembly, and budding.

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_15

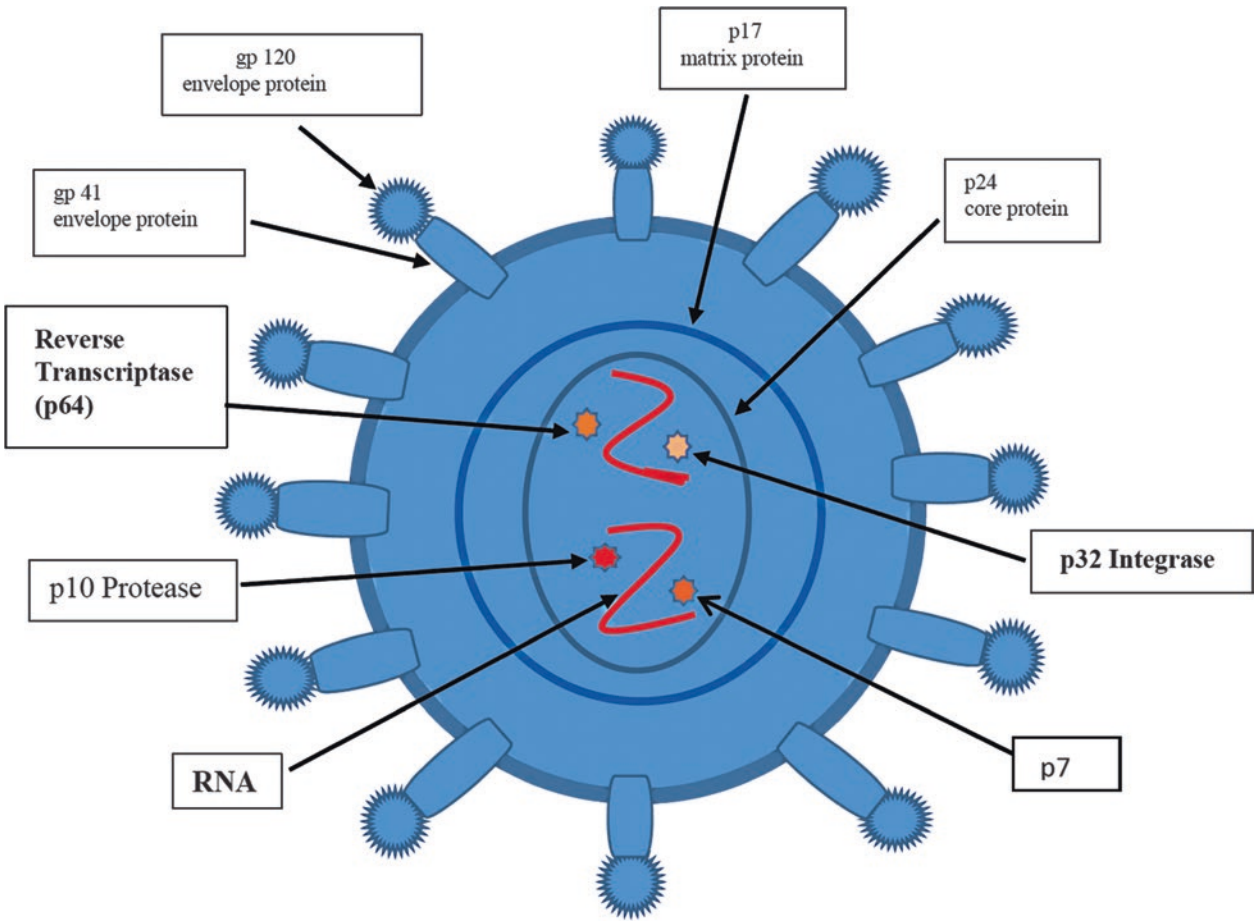


Fig. 15.1 Structure of HIV

Pathogenesis

Pathogenesis of HIV infection is complex, multifactorial, and incompletely understood. HIV infection's main target is the resting memory CD4 + T cell and selective depletion of CD4 + T cells is accompanied by aberrant activation of all the components of the immune system [12]. Immune activation is the major force that drives the HIV process and is associated with viremia and has a negative correlation with the CD4+ T cell count during chronic infection [13]. Cellular and soluble factors play an important role in acute and chronic immune activation and progression to AIDS [12–14] (Table 15.2 and Fig. 15.2).

Autoimmunity and HIV

The combination of immune dysfunction in patients with HIV infection and the development of autoimmune diseases is still incompletely understood. Autoantibodies are found with high prevalence in sera from HIV patients and may be fostered by a polyclonal stimulation of B cells.

Autoantibodies in HIV

- Anti-α-myosin
- Anti-EPO
- Anti-TPO
- Anti TSHR
- Anti-cardiolipin
- Anti-PS
- Anti-PI
- Anti-PC
- Anti-β2GPI
- Anti-prothrombin
- Anti-DNA
- Anti-RNP
- Anti-GBM
- ANCA

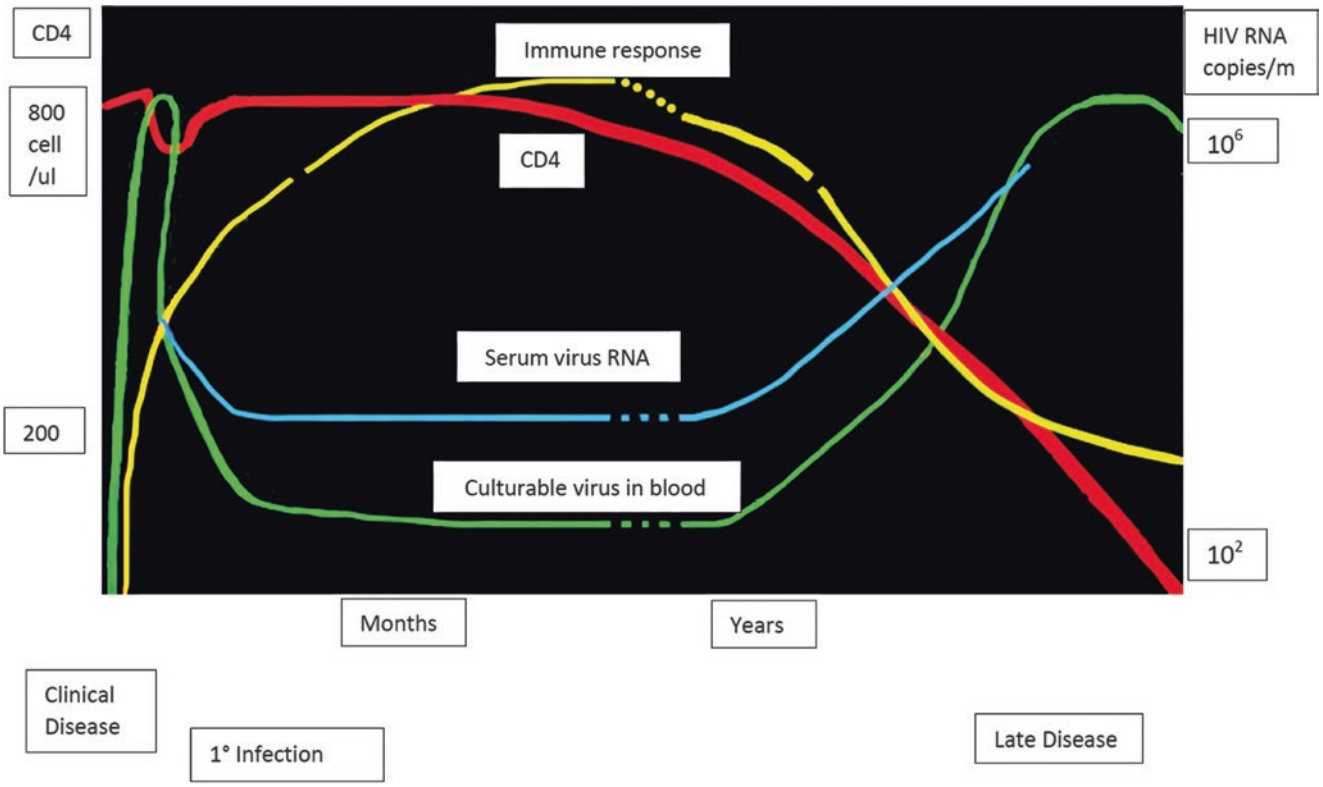
EPO erythropoietin, *TPO* thyroid peroxidase, *TSHR* thyroid stimulating hormone receptor, *PS* phosphatidylserine, *PI* phosphatidylinositol, *PC* phosphatidylcholine, *β2GPI* Beta 2 glicoproteína, *GBM* glomerular basal membrane.

Table 15.2 Cellular and soluble factors in immune activation

Innate	
Cells	Activation of macrophages and dendritic cells
Cytokines, chemokines	TNFα, IL-1, IL-6, IL-8, IL-12, IL-15, CXCL10, INFα
Acute phase proteins	Serum amyloide A, C reactive protein
Coagulation	D-dimers, tissue factor
Fibrosis	Activation of matrix metalloprotease, collagen deposition
Microbial sensors	Lipopolysaccharide binding protein, soluble CD14
Adaptive	
T cells	Increased turnover CD4+ and CD8+, CD4+ decrease, CD8+ increase and then decreases, formation of autoreactive CD8+, depletion Treg cell
B cells	Hyperactivation, hypergammaglobulinemia and immune complexes, autoantibodies

The presence of autoantibodies is associated with lower CD4+ T cell counts and increased mortality, which implies prognostic significance to this phenomenon in the context of HIV infection [15]. HIV immune dysregulation involving T or B cells or both may lead to autoimmune phenomena unique to HIV disease or to more classic autoimmune clinical syndromes.

Several possible mechanisms for autoimmune manifestations of HIV infection have been described, but molecular mimicry appears to be one of the most relevant. HIV virus has molecular similarity to self-antigens and may, therefore, induce antibody cross-reactions and lead to the development of autoimmune disease [16–18]. Whether autoimmunity is a component of natural immunity to HIV, its clinical significance and the role of neutralizing antibodies remain to be defined [16, 18].



Immune activation markers

TNFα	+++	+	+	+	++	+++
IL-6	+++	-/+	-/+	+	++	+++
sIL-2R	+++	-/+	-/+	+	++	+++
CD8-HLA-DR	+++	+	+	+	++	+++
CD8-CD38	+++	+	+	+	++	+++

Fig. 15.2 Natural course and immune activation markers of HIV

Autoimmune Mechanisms HIV

1. Direct effect of HIV: endothelial, synovial, hematopoietic cells
2. Increase cytotoxic cell activity
3. Increased expression of autoantigens
4. Molecular mimicry

Close to 40 years have elapsed since the onset of the HIV/AIDS pandemic and a total of 36.7 million individuals are living with the infection in 2016, including 1.8 million newly infected individuals, 1.0 million deaths, which includes 890,000 adults and 120,000 children under the age of 15 years, and 20.9 million living with HIV on antiretroviral therapy in 2017 [19]. Extraordinary progress in our understanding of pathogenesis, natural course, diagnostics, and combination antiretroviral therapy (cART) has occurred, which has led to a significant improvement in morbidity and mortality [20]. To date, the status of a considerable proportion of HIV/AIDS patients has changed from a near-fatal disorder secondary to opportunistic infections to a chronic disease in which cardiovascular, renal, diabetes, malignancy, and autoimmune co-morbid disorders have become prevalent and relevant [21–23]. The latter makes this topic of great relevance and importance to clinicians including rheumatologists and other practitioners dealing with this condition.

There are only a few longitudinal, descriptive, and comparative studies that allow with certainty define the impact of HIV infection during the pre-cART and post-cART eras, however, we will review and discuss available data on HIV infection and rheumatic manifestations.

Prevalence of Rheumatic Manifestations Before the Advent of cART Therapy

Winchester et al. first reported the association between HIV and rheumatic disease in 1987, when they described a series of patients with AIDS and Reiter's disease. Since that time, several reports have been published [24], and the prevalence of rheumatic manifestations among HIV infected patients ranges from 3% to 71% [25–29].

Arthralgia is the most common complaint, usually intermittent and polyarticular, with a reported prevalence between 1% and 79% [30]. **Myalgia** has also been frequently reported and difficult to separate from myopathy, so that the estimated prevalence rates may be misleading. Results of case-control studies revealed that myalgia is more common in HIV infected than in uninfected controls, with a frequency of 1.7–11% in the pre-cART while it increased between 0% and 77% in the post-cART. There are, however, other studies that showed the opposite; therefore, it is not clear whether therapy improves or exacerbates myalgia [31].

Painful Articular Syndrome

This syndrome is characterized by an acute onset and severe intensity of arthralgia presenting typically in one (usually large) joint in HIV-positive patients. It is of short duration (2–24 hours) and not associated with synovitis. It has an estimated prevalence of 10% among US patients in the late stages of the infection [26, 32] and a similar rate was observed among patients in Argentina [27]. This syndrome has not been reported in other case series from Africa and Asia continents [33–36]. The effect of cART on this syndrome is currently not well-defined.

HIV Arthritis

This syndrome is characterized by an acute onset of arthritis of large joints, non-erosive, lasting less than 6 weeks, absence of HLA B27 positivity and radiological changes, distinct from any other known rheumatic disease, with no known infective triggers, or other classical features. The prevalence rate ranges from 0.4% to 13.8% and most of these studies were performed in the USA. Most reports demonstrate that most cases occur in men, most commonly in the CDC stage IV of HIV infection [26, 27, 33, 37–42]. There is a cohort study from Africa where the reported prevalence was 82% [43]. Other African studies have not reported such high prevalence rates [44, 45].

Spondyloarthritis

Reactive Arthritis (ReA)

Most cases of ReA are associated with the late stages of immunosuppression seen in HIV-infected patients. The estimated prevalence of ReA in the pre-cART was as low as 0.02% to a high of 11%, variability depending on the sample studied. In the USA, two cohort studies performed through questionnaires, San Francisco Men's Health Study and the Johns Hopkins Multicenter AIDS Cohort Study, did not find an increase in ReA. However, most patients studied were in the early phase of HIV-infection [30, 31, 46].

In Latin American countries such as Mexico and Argentina, the frequency of ReA was found increased, while in Spain it was low. Mode of transmission appeared to explain the difference, with sexually-transmitted in Mexico and Argentina, and intravenous drug use in Spain [27, 38, 39, 47]. The low frequency of ReA has been reported in other cohorts in whom the mode of transmission was IV drug use [48].

Of great interest is the situation in Africa in which prior to the HIV pandemic ReA was rarely seen, which might be explained on the basis of the rarity of HLA-B27 [49, 50]. Following the advent of HIV, however, ReA became a com-

mon occurrence among HIV infected individuals with the majority being HLA-B27 negative [44]. Epidemiological studies in Zambia revealed that the presence of the allele HLA-B*57:03 confers a protective effect against the rapid progression of HIV [51].

Studies from Asian countries point out that ReA in HIV patients rarely occurs [36]. In this regard, mode of transmission of HIV appears to be similar in Asia and Africa, heterosexual, with a high prevalence of arthritogenic pathogens, which might suggest that other factors including genetics might play a role.

It can be concluded that ReA was relatively common in the western world pre-cART and its prevalence greatly diminished in the post-cART.

Psoriatic Arthritis (PsA)

A similar situation as in ReA occurs with PsA in which several studies on the pre-cART era revealed an increase in afflicted HIV infected patients. Rates of prevalence for PsA in HIV patients pre-cART was higher than in the general population, 0.4–5.7% vs. 0.25%, respectively [40, 52] and rates of incidence similar in both populations, 0.07%/annum vs. 0.05% [30, 46]. The populations studied, however, were in different stages of HIV infection. It should also be noted that patients with HIV and psoriasis had more severe and persistent lesions, and when compared with patients with classic psoriasis in HIV several morphological types can coexist in the same patient and that PsA was severe, deforming, erosive, and refractory to conventional therapy [53, 54].

The incidence and prevalence of both psoriasis and PsA in Africa are low even though black Africans have one of the risk alleles for psoriasis, HLA-CW6. This, however, drastically changed following the advent of HIV in which both disorders were increasingly recognized in African populations [55, 56]. Asian populations have a low prevalence rate of psoriasis and PsA, but this also changed following the HIV pandemic. Post-cART, both disorders have greatly diminished in Africa and Asia.

Ankylosing Spondylitis (AS)

AS, the prototype of the spondyloarthritides, is more common in the western world [57] and much less common among sub-Saharan Africans where the frequency of HLA-B27 is very low (<1%). The frequency, however, of HLA-B27 in West Africa is higher 7.8–9.7% [58, 59], but despite this higher prevalence AS is rarely seen in this region. This, however, changed following the onset of HIV in which several reports describing the association were reported from African populations.

In general, there have been few reports of AS in HIV infected patients and reported data might suggest that AS is uncommon in HIV. But it is probable that most patients with HIV or AIDS are classified as having undifferentiated spondyloarthritis in the absence of radiographic or HLA-B27 testing or the paucity of long-term follow-up studies.

Rheumatoid Arthritis (RA)

The immune dysregulation inherent to HIV infection and its clinical manifestations may mimic or interfere with a diagnosis of rheumatoid arthritis. HIV patients may exhibit symmetrical polyarthritis, which tends to be seronegative for the most part. However, erosive forms and seropositive for rheumatoid factor (RF) have also been described [60]. On the other hand, the presence of low titer RF and CCP antibodies in patients with HIV may lead to an erroneous diagnosis of RA. HIV patients may also exhibit a high proportion of RF and CCP antibodies, which decrease after initiation of cART suggesting that HIV is capable of inducing autoantibodies. Follow-up studies, however, of this HIV population does not reveal the development of RA [61–64]. In addition, it is well recognized the presence of false-positive HIV serology in patients with RA suggesting a cross-reactivity between HIV diagnostic tests in patients with RA [65]. Another important issue was the impact of de novo HIV infection in established RA [66, 67]. An early observation in the pandemic was that most RA patients might go into remission after the development of AIDS. However, the presence of active RA disease including radiological progression can be seen despite a profound state of immunosuppression [68, 69]. Also, development of de novo RF and CCP antibodies positive RA can be seen in well control HIV infection (normal CD4 cell count and negative HIV viral load), and RA disease activity behaves in identical fashion as in RA seen in HIV negative individuals.

Therapy for HIV patients affected with RA as well as for most connective tissue disorders is not well defined, but most can be safely treated in identical manner as in the non-HIV afflicted population. Caution, however, and prophylaxis for opportunistic infections, should be exerted when immunosuppressive or biologic therapy is used.

Systemic Lupus Erythematosus (SLE)

SLE has been rarely reported in association with HIV infection, but it represents a diagnostic and therapeutic challenge, especially when they co-exist in the same patient. HIV impacts on SLE in diagnosis and assessment of disease activity. HIV infection and SLE shares several clinical features and laboratory findings, which can make the diagnosis extremely difficult. A variety of constitutional manifestations such as fever, arthralgia, arthritis, myalgia, skin rash, lymph node enlargement, cytopenias, pulmonary, cardiovascular, renal, and CNS involvement can be observed in both active

SLE and HIV infection. A variety of autoantibodies including ANA, anti-dsDNA, anti-Sm, and anti-cardiolipin antibodies can be seen in both disorders. But hypocomplementemia secondary to HIV has not been described, and this finding may be used to distinguish lupus activity from HIV infection [70, 71]. Diagnostic tests for HIV have been reported as false-positive results in SLE patients and multiple studies have reported autoantibodies reactivity to HIV p18 and p24 antigens. These findings make necessary the need to perform confirmatory tests, such as viral RNA PCR or HIV-Western Blot assays [72].

HIV infection, as described in RA, may have an important effect on the natural course of SLE. The decrease in CD4 lymphocytes might ameliorate SLE disease activity and induce remission. However, SLE disease activity may persist during HIV infection and not related to the use of cART [73–75].

Lupus may also impact on HIV infection. Homology between self-antigens in lupus patients and viral proteins has been identified. Antibody production including neutralizing antibodies might develop during SLE may confer protection against HIV infection by molecular mimicry mechanisms [76]. In addition, antimalarial drugs such as chloroquine and its derivatives, which are used in SLE therapy, may have anti-HIV activity. A potential role for interleukin-16 in the observed low incidence of HIV infection in patients with SLE has been described [77].

Treatment of SLE with glucocorticoids and immunosuppressive drugs is challenging because they may trigger viral replication and rapid progression of the disease. On the other hand, the use of cyclophosphamide in lupus flares may also result in an increase in the viral load. Viral load becomes undetectable when cyclophosphamide is discontinued. Therefore, treatment of active lupus should be individualized and should be aimed at reaching a balance between HIV infection and lupus activity.

The association of HIV-related discoid lupus and HIV has rarely been reported and the few cases described have occurred after the onset of cART and in association with undetectable HIV viral load and normal CD4 T-cell count [78].

Anti-Phospholipid Antibody Syndrome (APS)

Presence of anti-phospholipid antibodies including anti-cardiolipin and lupus anticoagulant antibodies is seen in most HIV patients, 60–70%. However, the development of clinical manifestations characteristic of APS is uncommon, and only a handful of cases have been reported in the literature. Other anti-phospholipid antibodies such as anti-B2 Glycoprotein I appear to have a lower frequency [31, 79].

Systemic Sclerosis (SSc)

The association between HIV infection and SSc is rare. There are only a few reported cases. Two male patients developed localized scleroderma after several years of cART. Two other patients developed symptoms of diffuse systemic sclerosis. One of the two cases in the background of immunosuppression and responded well to therapy with steroids and cART. The other patient developed symptoms of SSc 7 years after HIV infection and cART and with good virologic suppression and normal CD4 cell count [80–82].

Polymyositis and Dermatomyositis

These diseases have rarely been reported. The prevalence of polymyositis is reported as 0.22% and dermatomyositis occurs less frequently, and when present can occur at any stage of HIV infection. HIV-associated polymyositis usually has mild disease activity, which is often difficult to recognize, especially in a population that frequently manifests generalized weakness and a debilitating course. Both polymyositis and dermatomyositis carry a relatively good prognosis, responds well to glucocorticoids and immunosuppressive therapy [83, 84].

Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

DILS was initially identified in 1985 as lymph node hyperplasia and parotid gland enlargement in HIV-positive patients. Later, in 1989, this complex was named “diffuse infiltrative lymphocytosis syndrome”. Early criteria proposed by Itescu et al. for the diagnosis of DILS required salivary gland enlargement or xerostomia for >6 months and lymphocytic infiltration of the affected gland confirmed by biopsy [85].

Diagnostic Criteria for DILS (Itescu et al. [85])
Requires All Criteria

1. HIV infection (positive serology)
2. Bilateral salivary gland enlargement or xerostomia
3. Persistence of signs/symptoms for 6 months or more
4. Histologic confirmation of salivary or lacrimal gland lymphocytic infiltration without granulomatosis or neoplastic involvement

Table 15.3 Features of DILS

Feature	
Lymphocytic infiltration	CD8+ T cells
Sicca symptoms	Present
Glandular manifestations	Moderate to severe parotid enlargement
Extra-glandular manifestations	Present
Autoantibodies	Rarely present, exceptional low frequency of RF, ANA, anti-Ro
HLA association	DR5(DR11), DR6(DR13), B45, B49, B50

HIV-related DILS is characterized by salivary and lacrimal glandular swelling and sicca symptoms of varying intensity. Prevalence of this complication is highest among African Americans (up to 48% of infected individuals) and is associated with HLA class II alleles (DRB1) that are not seen in other racial groups with DILS, and it occurs in patients whose disease is at less advanced stages [86, 87]. The syndrome usually presents as a Sjögren-like illness that generally associates with sicca signs with bilateral parotid gland swelling, lymphadenopathy, and extra-glandular organ involvement. DILS is also characterized by CD8+ T cell infiltration, lack of autoantibodies (anti-Ro and anti-La), although they may be present in some exceptions, and extra-glandular visceral infiltration. The lung, being the most common extra-glandular organ involved and when affected it presents as a lymphocytic interstitial pneumonitis (LIP)[86, 88]. Its natural history has also changed since the introduction of cART, and it is less frequently seen including the extra-glandular manifestations such as LIP [87, 89].

Chen et al. conducted a nationwide population-based study in the Taiwanese population and showed that the incident rate of DILS was 0.56/1000 person-years higher compared with the general population, and the incidence was higher in patients without cART than in patients with cART, supporting the notion that HIV intervenes in the pathogenesis of DILS and that cART reduces the risk of acquiring DILS [90, 91]. Other clinical and laboratory features of DILS are shown in Table 15.3.

DILS patients with mild symptoms may not require specific treatment, but glucocorticoids or immunosuppressive drugs should be considered for patients with progressive glandular involvement.

Vasculitis

The entire clinical spectrum and size of involved blood vessels can be seen in HIV-associated vasculitides. The incidence of vasculitis in HIV infection is relatively low at 1%. Its presence, however, varies according to ethnic origin and it appears to have a higher prevalence in Orientals. Vasculitis has been reported in patients infected with HIV more commonly in those with a profound stage of immunosuppression (CD4+ < 200/μl), in some associated with hepatitis B infection, but has also been reported in early HIV stages (>500 μl) [92, 93].

Table 15.4 Features of HIV-PAN

Feature	
Virus-associated	No associated HBV
Involvement	Rare multisystem
Common symptoms	Peripheral neuropathy, rash
Clinical course	Usually not progressive or fulminant, nonlife-threatening

As it has been described with other rheumatic manifestations, factors such as ethnic origin and route of transmission might be implicated in its prevalence. Zhang et al. have reported a high prevalence of vasculitis when compared to other rheumatic syndromes. They reported 20 cases of vasculitis in a cohort of 98 Chinese patients and the main route of transmission in their population was blood transfusion. A variety of syndromes were reported including Behçet-like disease, Henoch-Schonlein purpura, digital gangrene, and central nervous system vasculitis [36].

Polyarteritis nodosa (PAN) is the most prevalent form of vasculitis coexistent with HIV infection, and it is not related to hepatitis B infection like the classic form, and can occur at any stage of HIV disease. The clinical course of HIV-related PAN exhibits major differences in comparison with classic HBV-related and it is clinically less aggressive, and peripheral neuropathy is the most common clinical manifestation [94, 95] (Table 15.4).

Presence of anti-neutrophil cytoplasmic antibodies, especially pANCA, is high (13–42%), but its clinical significance is not well defined. cART plays a beneficial role in its treatment due to a direct role of HIV in the pathogenesis of PAN. On the other hand, the impact of other viruses including hepatitis B, hepatitis C, cytomegalovirus (CMV), Epstein-Barr (EBV), and varicella-zoster virus (VZV), which often coexist in HIV positive individuals is not fully characterized [23, 94, 96].

Glucocorticoids have been successfully used in many cases of HIV-associated vasculitis and immunosuppressive drugs should be reserved for resistant patients.

Other forms of vasculitis such as Henoch-Schonlein purpura might occur secondary to various infectious triggers. ANCA-associated vasculitis is extremely rare in HIV infected patients [23].

Cryoglobulinemia may coexist with HIV infection. Its presence is usually asymptomatic and responds well to cART regimen [86]. In the cART era, HIV-infected patients have been shown to have decreased levels of serum cryoglobulins [95, 97, 98].

Septic Arthritis

Osteoarticular infection due to pyogenic bacterial does not occur more frequently in patients with HIV infection as compared with the general population. The incidence of musculoskeletal infections in patients with HIV appears to be low (0.3–3.5%). Case series reported from the USA, Europe (Italy), and Africa have shown that septic arthritis occurs less frequently in HIV patients [99–101]. There are retrospective HIV cohort studies that show a relatively low risk of septic arthritis [102, 103]. Marquez et al. studied prospectively 75 patients with HIV infection referred to a rheumatology clinic in New Orleans and reported prevalence of septic arthritis and osteomyelitis in 8% and 20%, respectively. Atypical mycobacterial (mycobacterium haemophilum and Kansasii) and fungal (candida and sporotrichosis schenckii) infections rarely occur except in advanced HIV infection (CD4 count less than 100/mL).

Rheumatic Disorders in the Combination Antiretroviral Therapy (cART): Future Trends

Introduction of cART in the management of patients infected with HIV marks a milestone in the history of medicine because it led to a significant change of the natural history, long-term outcome, occurrence of comorbidities, and as importantly a drastic reduction in mortality.

A significant decline in inflammatory rheumatic complications has been observed following the introduction of cART [90, 99]. And of great interest and importance, a new group of rheumatic disorders has emerged covering the spectrum of systemic autoimmune and autoinflammatory diseases, posing new clinical challenges [90, 99] (Table 15.5). Currently, three diseases deserve special attention: avascular necrosis, osteoporosis, and immune reconstitution inflammatory syndrome.

Table 15.5 HIV and autoimmune/non-autoimmune diseases

Pre-cART	Post-cART
Connective tissue diseases	Avascular necrosis
DILS	Osteopenia/osteoporosis
Myositis	IRIS
Vasculitis	Sarcoidosis
	Graves' disease
Arthritis	Autoimmune hemolytic anemia
Reactive arthritis/psoriasis	Autoimmune thrombocytopenia
HIV related	Uveítis
	Inflammatory bowel disease
	Psoriasis

Changes in the Prevalence of Inflammatory Rheumatic Diseases

Prior to the introduction of cART, reactive arthritis, psoriatic arthritis, and the painful articular syndrome were the most common rheumatic disorders observed in HIV-infected patients. However, after the introduction of cART, the incidence of these diseases decreased dramatically and new forms of rheumatic diseases appeared [99].

Calabrese et al. conducted a longitudinal cohort study and demonstrated post-cART a decline in ReA, PsA, and myositis [104]. Marquez et al. reported a rise in septic disorders and malignancies and a decline in spondyloarthritis [41]. DILS was also affected by cART. Basu et al. reported a decline in the incidence of DILS [86], but Mastroianni et al. reported opposite results [105]. As previously mentioned, Chen et al. reported that cART reduced the risk of acquiring DILS [91].

In contrast, Parperis et al. did not observe a higher risk of rheumatic diseases except avascular necrosis (AVN) and psoriasis [106]. Similar findings were reported by Yang et al. who showed that the prevalence of autoimmune arthritis among HIV infected patients was similar to that of the general population [107].

A recent study performed in the UK assessed 364 HIV-positive patients with musculoskeletal symptoms between January 2005 and December 2012. Majority of patients (85%) referred had no evidence of an inflammatory rheumatic disease but instead were diagnosed with regional musculoskeletal pain, specific soft tissue disorders, chronic widespread pain or osteoarthritis. Among the remaining 15%, most inflammatory diagnoses were not made more often than would be expected for the general population, except for spondyloarthritis [108].

There are few studies dealing with the incidence, prevalence, and chronology between rheumatic disorders associated with HIV infection and AIDS. Two large studies, one from Taiwan and the second from France, merit discussion [90, 109]. In the first study, Yen et al. reported on the incidence of AIDS in a nationwide HIV/AIDS patient (PLWHA) cohort in Taiwan and compared it with the general population; standardized incidence rates (SIRs) were higher for incident Sjögren's syndrome, psoriasis, SLE, autoimmune hemolytic anemia (AHA), and uveitis. An interesting observation was the lower risk for development of AS despite a high prevalence of HLA-B27 in Taiwanese people (5%). In contrast, PLWHA who received cART had higher SIRs for psoriasis, AHA, and uveitis, while those that did not receive cART had higher SIRs for Sjögren's syndrome, psoriasis, RA, SLE, and other autoimmune disorders. Lebrun et al. also conducted an epidemiologic study in a French nation-wide HIV cohort to estimate the prevalence of 26 inflammatory and autoimmune diseases

(IADs) among patients living with HIV (PLHIV) in the cART era (from January 2000 to July 2013), and to describe their occurrence according to cART onset, the immune-virological status and hepatitis C virus (HCV) and/or hepatitis B virus coinfection. Results showed that several IADs including psoriasis, sarcoidosis, RA, AS, Grave's disease, AHA, immune thrombocytopenia, and chronic inflammatory bowel disease were the most prevalent diseases. Majority of patients (59%) developed IAD after HIV infection with a mean delay of 10.6 + −6.4 years. In addition, patients developing IAD after the diagnosis of HIV infection, 572 (70%) were on cART and 419 of them (73%) had undetectable HIV viral load. Comparing data from Taiwan and French studies, some geographical variability in terms of IADs is observed, but both studies confirmed previous reports in the literature concerning the relationship between HIV/AIDS and rheumatic disorders.

Immune Reconstitution Inflammatory Syndrome (IRIS)

A resurgence of autoimmune disorders may occur following the introduction of cART due to the restoration of immune competence. This phenomenon known as IRIS is linked to a rapidly recovering immune system, and it appears directly related to an increase in CD4+ T cells, CD8+ T cells, CD4+:CD8+ T cell ratio, and an increased cytokine levels [110] (Fig. 15.3). IRIS may develop in the following manners:

A. "Paradoxical IRIS"
   In this subset, affected individuals develop symptoms and signs associated with a known opportunistic infection (OI) for which treatment is underway and exacerbate despite an earlier clinical response to therapy prior to ART.
B. "Unmasking IRIS"
   Patients on this subset experience a new OI with a marked inflammatory component following initiation of ART. Recent reports, however, have defined all-new OI in the first 6 months of ART as cases of unmasking IRIS.

Several classification criteria for IRIS have been proposed, but none has been validated. The reported incidence of IRIS varies widely from 6.4% to 37.7% depending on the offending microorganism involved [111, 112].

IRIS is not only associated with a new infection or exacerbation of quiescent infections but also may occur as either new appearance or an exacerbation of a previously quiescent or occult autoimmune syndrome [41, 104]. Calabrese

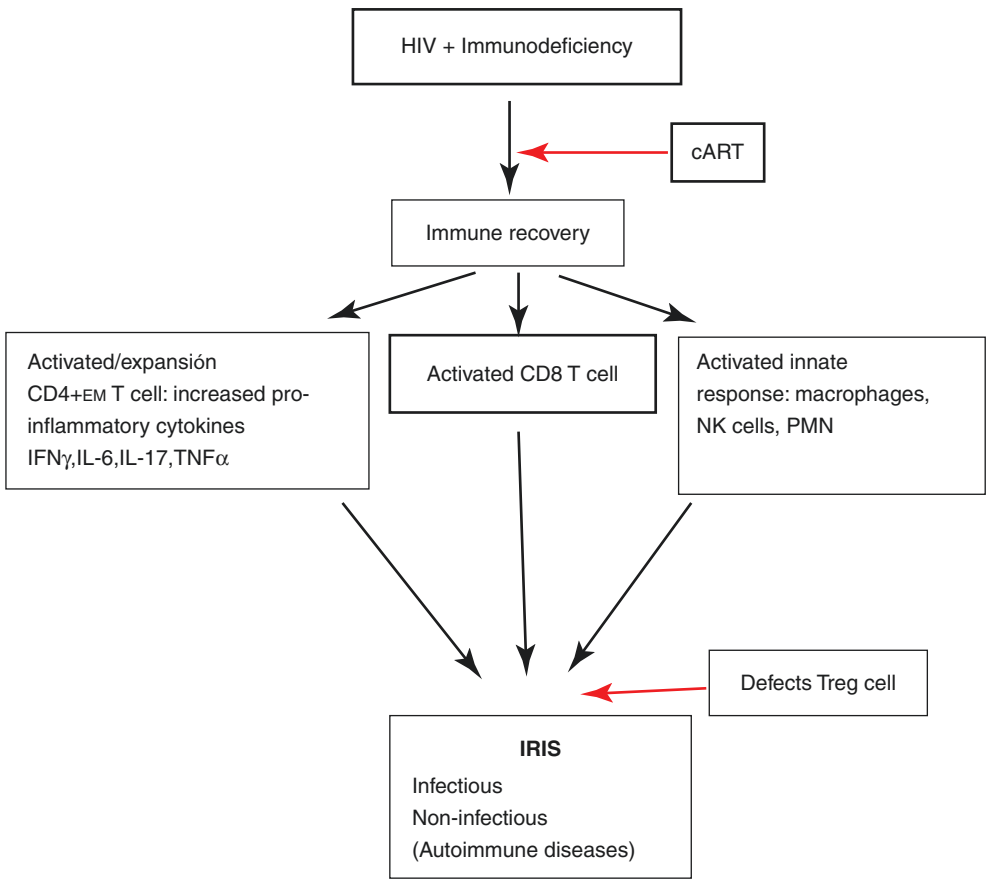


Fig. 15.3 Pathogenesis IRIS

et al. conducted a prospective, longitudinal cohort study and described 32 cases associated with IRIS including sarcoidosis, RA, and SLE [104].

IRIS symptomatology may ensue days to months after ART begins, and most cases resolve spontaneously, but at times they can become life-threatening in severity, necessitating other therapeutic interventions. It is, however, usually not necessary to discontinue cART during this time. IRIS is generally self-limiting and should not require lifelong therapy [41, 104, 111, 112].

Osteoporosis

As the life span in HIV-infected individuals increases, new comorbid conditions develop, including osteopenia and osteoporosis, with an increase in the risk of bone fractures. It is estimated that 2 out of 3 HIV infected individuals have osteopenia, and they also have 3.7 times more risk of developing osteoporosis than non-HIV infected individuals [113]. The estimated prevalence of osteoporosis in the HIV population is 15% and of osteopenia 52% [114]. This decrease in bone density is between 2% and 6% during the first 2 years of cART [115, 116]. The rate of fracture in the HIV population is between 30% and 70% compared with control non-HIV population [117–120].

In addition to the classic osteoporosis risk factors, other HIV-specific risk factors such as the same defined AIDS history, low CD4+ cell count, coinfection with hepatitis C, and antiretroviral therapy may all contribute to the increased risk in osteoporosis [118, 119].

There is no specific guide for the management of HIV patients with decreased bone density, and HIV patients are not included in the list of patients at risk in the osteoporosis management guidelines [121]. However, there are two instruments, BMD or the application of FRAX, that can be used for the assessment of HIV patients with this problem, especially when treatment is considered in the presence of osteopenia. It should be kept in mind, however, that the FRAX has not been validated for the HIV-positive population [122].

Regarding therapy, in addition to adequate nutrition including calcium and vitamin D and modification of lifestyles, pharmacological therapy with bisphosphonates, alendronate, and zoledronic acid, have been shown to have a positive effect on BMD and tolerability similar to those found in the general population [123–126]. Other therapies have not been evaluated.

Avascular Bone Necrosis (AVN)

Osteonecrosis (AVN) is another complication associated with HIV infection, and when it affects hips or any other major joint might lead to severe disability. Its incidence has been estimated to be 10 times compared to the general population [127, 128]. Prevalence also increases by almost 5% and is similar to the prevalence reported in patients at high risk for osteonecrosis in the context of a variety of underlying diseases [129].

Etiology of this complication is poorly understood, and little is known about potential risk factors in HIV patients. Use of glucocorticoids and hyperlipidemia contribute to osteonecrosis seen in HIV patients, but further studies are needed to fully characterize other potential risk factors for this complication [130, 131].

Approach to Therapy of Rheumatic Disorders in HIV-Infected Patients

The introduction of cART has had a profound effect on morbidity and survival in HIV-infected patients and the converse is also correct, HIV infection has also impacted a great deal on the natural history and therapeutic intervention of autoimmune diseases due to the presence of the underlying immunosuppression state and that complications can occur when immunosuppressive drugs or biologic agents are administered because they may lead to serious complications including infections [132].

Treatment of autoimmune diseases (AIDs) is similar in HIV-positive and HIV-negative patients. A significant proportion of HIV-associated AIDs including inflammatory musculoskeletal involvement respond well to conventional therapy such as NSAIDs, narcotic drugs and DMARDs, but refractory cases may need the use of biological agents, especially TNF inhibitors [133]. The use of these agents may represent a challenge, especially in patients with co-existent hepatitis infection, but published reports indicate that in the presence of stable CD4+ T cell counts and low viral loads their use can be both safe and efficacious. When considering immune suppressive therapy, it is important to keep in mind that CD4+ T cells are necessary in the control of intracellular and extracellular bacteria, parasites, and viruses, and the presence of TNF is needed and useful for controlling infection, and its increase favors replication of viral particles.

Rates of serious infections in HIV-infected patients treated with TNF-α inhibitors for concomitant AIDs are comparable to those observed in RA patients receiving TNF-α inhibitors [134].

At present, biologic agents and other DMARDs (including methotrexate, leflunomide, mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclosporine) are recommended when patients have CD4+ T cell counts above 200 cells/mm3 and HIV viral activity completely suppressed [108, 135, 136]. Glucocorticoids, hydroxychloroquine, and sulfasalazine have been shown to be safe and well-tolerated [96]. Currently, however, there are no studies of good quality on the use of biologic therapy to treat inflammatory disorders in HIV-infected individuals; therefore, we cannot conclude on efficacy and safety of biologic therapies in HIV-infected populations [137].

Prophylaxis of Opportunistic Infections While on Immunosuppressive Therapy

HIV patients on immunosuppressive therapy have an increased risk of infection reactivation. Close attention to the association between tuberculosis, varicella zoster, and opportunistic infections such as *Pneumocystis jirovecii* (PJ) should be kept in mind [135, 138]. Patients should be screened for HIV viral load, HBV, HCV, TB, and other infections according to endemic geography [139].

There are no guidelines with regard to the use of synthetic disease-modifying anti-rheumatic drugs (sDMARDs) and biologics in patients with a history of hepatitis B and hepatitis C infections. With regard to PJ, there are no consensus guidelines for the prophylaxis of PCP in connective tissue diseases [140].

Prophylaxis for TB is recommended and it should follow the CDC guidelines. It is recommended to screen for latent TB prior to initiating chronic therapy with glucocorticoids, and chemoprophylaxis with either isoniazid (INH) for 9 months or rifampicin combined with INH for 3 months should be initiated in the presence of latent TB infection (LTBI) [141, 142].

Conclusion

Autoimmune and other inflammatory rheumatic disorders can occur in patients with HIV infection in the presence of poor or good immune-virological control under cART. Some AIDs are more prevalent according to cART and the cohort studied. In general, AIDs appear following diagnosis of HIV infection and also under cART, and clinical manifestations observed in the HIV population are similar to those seen in the general population. Glucocorticoids and other immunosuppressive agents seem to be effective and well-tolerated, but prophylaxis of infection is very important. Comorbidities such as osteoporosis and AVN appear as a consequence of the aging of the HIV-infected population and appropriate preventive measures should be taken. While the pathophysiology of HIV-related autoimmune rheumatic diseases is not well understood, the intricate enigma of this association merits further investigation.

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HTLV-1: A View from the Rheumatologist

16

Alejandro Fuentes and Paula I. Burgos

Introduction

There are four human T-cell lymphotropic viruses described (named HTLV-1 to HTLV-4), but only HTLV-1 and HTLV-2 are associated with infection in humans [1]. The human T-cell lymphotropic virus type 1 (HTLV-1) is part of the genus *Deltaretrovirus* of the subfamily *Orthoretrovirinae* of the family of retroviruses [2] and was the first human retrovirus discovered [3]. There are six known subtypes (A to G), with cosmopolitan subtype A being the most common in infections [4, 5]. The modes of transmission in order of effectiveness are the following: (1) transfusion of non-leukocyte depleted contaminated cellular blood products (up to 64%), (2) mother to child transmission (10–25% by breastfeeding, especially more than 6 months, and 3–5% with transplacental exposure), and (3) sexual intercourse (1% per year in serodiscordant couples, mainly from male to female) [4, 6–9]. The use of common needles and organ transplantation are also supposed to be mechanisms of transmission [10–13].

Epidemiology

There are approximately 10–20 million people infected worldwide [4, 14], and 90–95% of them remain as asymptomatic carriers [5]. There may be an underestimation of the global prevalence of HTLV-1 infection because serological screening is made basically in healthy blood donors and pregnant women [1, 5]. In children, the prevalence of the infection increases from 2 years of age getting stable during puberty [15], and in adults the prevalence increases with age being higher in females than males [7]. This is because of the known ways of transmission: prolonged breastfeeding and sexual intercourse (with higher transmission from males to females), respectively [7]. Interestingly, there is a geographic distribution with clusters of high prevalence, with a tendency of being in the same latitude, besides areas of medium or low prevalence. The most important highly endemic areas are some islands of southwest Japan such as Shikoku, Kyushu, and Okinawa with up to 37% of seroprevalence [5]. Some Caribbean islands and Sub-Saharan African countries such as Benin, Cameroon, and Guinea-Bissau show prevalence close to 5% [5, 16, 17]. In South America, there is some correlation in places with the same latitude and altitude (near the coasts), with a prevalence of 1–5% in countries such as Brazil, Perú, French Guyana, or Colombia, and less than 1% in Chile and Argentina [5, 18–20]. Other isolated highly endemic areas are the Mashad region in Iran, some aborigines in the north of Australia, first-nations in North America, and Romania in Europe [4, 7, 21]. Of note, molecular and genomic studies of the Cosmopolitan Subtype A, which is endemic in Japan, the Caribbean, South America, North and West Africa, and the Middle East, suggest dissemination from a common ancestor [4].

Spectrum of the Disease

As described above, about 90–95% of patients infected by HTLV-1 are asymptomatic carriers. Among those who will present a condition, the manifestations include the following: (1) adult T-cell leukemia/lymphoma (ATLL) in 2–6% [22], (2) HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in 2–3% [6, 7, 23], and (3) other inflammatory conditions such as arthritis, uveitis, Sjögren's syndrome, dermatitis, thyroiditis, bronchiolitis-alveolitis-pneumonitis, myositis, nephritis and hepatitis – cholangitis (without exact data of the prevalence or incidence of these manifestations) [5, 24–28]. Of interest, the superinfection of HTLV-1 virus with *Strongyloides stercoralis* (a gastrointestinal parasite) predisposes the appearance of ATTL in those patients [29].

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_16

Virus Characteristics, Pathophysiology, and Mechanisms of Damage

HTLV-1 has two relevant proteins: Tax and HBZ. Tax (p 40) is an important protein in viral transcription that also has the particularity of modifying transduction pathways of the infected cell such as NF-kB, CREB, SRF, NFAT, and AP-1; this leads to the transactivation of genes that code for IL-2 receptor α chain (CD25), interferon-γ, and intercellular adhesion molecule 1 (ICAM1) [7, 30–36]. HBZ can act as a microRNA promoting the function of the transcription factor E2F1 and the proliferation of the infected cell; as a protein produces decreased expression of Tax [37, 38].

CD4+ T lymphocytes (CD4+ TLs) have a pivotal role in HTLV-1 infection and can change their behavior leading to activation, cell proliferation, and cytokine synthesis in response to viral proteins [39]. CD4+ TLs infected with HTLV-1 produce the C-C motif chemokine 22 (CCL22) which can attract other CD4+ TLs that express CCL22 receptor (CCR4+) in their surface, making CD4+ CCR4+ TLs the main infected cells [40, 41]. Indeed, the above mechanism has emerged as an interesting therapeutic target [42]. HTLV-1 promotes a TH1 phenotype response, with increased levels of IL-2, IL-6, Interferon gamma (IFN-γ), and TNF alpha especially in the spinal fluid and blood of patients with HAM/TSP [43, 44]. The Tax protein has been shown to affect the above-described transcription factors and cellular cascades such as Rho-GTPases and the JAK/STAT pathway [28, 31, 38].

The regulatory T lymphocytes (Tregs) are CD4+ T lymphocytes that express the forkhead box protein P3 (FOXP3) transcription factor and have the peculiarity of inhibiting the activation of other lymphocytes [45]. Alterations in the expression of FOXP3 have been linked to the presence of inflammatory diseases [46]. In HAM/TSP and ATTL, it has been observed that HTLV-1 increases the expression of FOXP3 by means of Tax, causing a diminished antiviral response because of lower activity of the CD8+ cytotoxic T lymphocytes (CD8+ CTL) [47]. On the other hand, the underexpression of FOXP3 could lead to a more inflammatory CD4+ T lymphocyte phenotype [7, 41].

CD8+ CTL can recognize Tax protein as the main antigen of HTLV-1 and suppress viral activity [48], but an excess in their activity has been also linked to inflammatory damage in the host [49]. Data from Japan suggest that certain HLA I alleles could confer to CTLs a different quality in their response: *HLA-A∗02* or *HLA-Cw∗08* can act as protective decreasing proviral load and the risk of HAM/TSP in infected patients, while *HLA-B∗54* could stimulate an inefficient phenotype to CTLs, making them proclive to inflammatory damage in the host and increasing the risk of HAM/TSP [49–51].

Data about the mechanism of inflammation and damage in HTLV-1 infection come mainly from HAM/TSP studies. The "innocent bystander" is the most accepted hypothesis [52, 53]: CTLs are the main responsible for the tissue damage in the presence of HTLV-1-infected CD4+ TLs, with an important role of IFN-γ and in a lesser extent, TNF alpha and IL-6 [6, 7, 54, 55].

HAM/TSP

Risk Factors and Neuropathology

The risk factors for the development of HAM/TSP are listed in Table 16.1, being proviral load the strongest predictor [50, 56–58]. In neuropathology, there are mononuclear infiltrates in the central nervous system (CNS) predominantly in the upper thoracic spinal cord and around the blood vessels [59, 60]. CNS develops a loss of spinal cord volume at months or years from the beginning of the disease [61].

Clinical Course

The clinical picture corresponds to a chronic or subacute history of weakness and stiffness of lower extremities, with frequent falls and problems with climbing stairs or rising from a chair [6, 7]. Often, there is neuropathic lumbar pain which can radiate down to one or both legs, lower limbs paresthesia, sphincter disorders such as constipation or urinary incontinence/retention, and erectile dysfunction in males [7, 69, 70]. The physical examination shows spastic gait and bilateral lower limb hypertonia, hyperreflexia (clonus of one or both ankles can be present), and extensor plantar reflex; sensory signs are unusually seen [71, 72]. Data from a study of 123 patients from the Caribbean isle of Martinique showed

Table 16.1 Principal risk factors for development of HAM/TSP

Proviral load	More than 1% of DNA copies per 100 peripheral blood mononuclear cells (PBMCs) [57, 58]
Patient genetics	HLA class I genotype *HLA-DRB1∗0101* [62] *HLA-B∗07* [63] *HLA-B∗54* [56] Single Nucleotide Polymorphisms (SNPs) *IL-6* – 634C [50, 51] *TNF* – 963A [63]
Demographics	Female gender [6, 64] ≥50 years old [6, 65]
Route of transmission	Blood transfusion [66] Solid organ or bone marrow transplantation [67, 68]

that from the onset, the median time to use a walking aid was 6 years and the median time to use a wheelchair was 21 years. Patients more than 50 years old at onset and a high HTLV-1 viral load were predictors of rapid evolution to the use of the aids named above [73].

Laboratory Studies

The presence of positive HTLV-1 antibodies from an enzyme-linked immunoassay (ELISA) requires confirmation by western blot or detection of viral nucleic acid [6, 7]. A lumbar puncture analysis can show a normal or nearly normal protein concentration and mononuclear count in cerebrospinal fluid (CSF); also, there could be a higher HTLV-1 viral load in CSF lymphocytes than peripheral blood mononuclear cells (PBMCs) [74]. On plasma, a profile of elevated concentrations of β2 microglobulin and calgranulin B and low apolipoprotein A2 levels can differentiate HAM/TSP of asymptomatic carriers [75]. On brain MRI, there can be asymmetrical periventricular and/or subcortical white matter lesions which look different from alterations seen in multiple sclerosis; as mentioned above, compromise of the spinal cord is cervical and thoracic areas with atrophy in chronic stages [76, 77]. The presence of T2 hyperintensity in the spinal cord on MRI study suggests a rapidly progressive clinical course [78].

Diagnosis of HAM/TSP

A progressive spastic paraparesis with impaired gait (with or without sensory or sphincter abnormalities), the presence of HTLV-1 in serum or CSF and the exclusion of other conditions that can resemble HAM/TSP are necessary for a *definite* diagnosis. If in the previous clinical picture is observed isolated lower limb spasticity/hyperreflexia or isolated Babinky sign (with or without sensory or sphincter abnormalities) instead of the progressive spastic paraparesis, the diagnosis is *probable*. When any clinical feature described above is present and HTLV-1 is positive in serum or CSF but other conditions that can mimic HAM/TSP have not been ruled out, the diagnosis is *possible* [79].

Treatment of HAM/TSP

The use of baclofen and botulinum toxin injections for spasticity [80, 81]; gabapentin, pregabalin, or tricyclic antidepressants for neuropathic pain [82]; physical therapy for motor disturbances; and specific treatment of sphincter disorders are examples of the symptomatic approach for management of HAM/TSP [83].

Regarding drugs trying to modify the natural history of the disease, studies have been focused on diminishing the HTLV-1 proviral load or to modify the immune response of the host. Corticosteroids (CS) are often used in recently onset (≥3 years) or progressive HAM/TSP, especially in the beginning of the disease. Results are seen on motor disability but data about other issues such as sphincter disorders or neuropathic pain is scanty [6, 7, 84, 85]. Oral CS have been useful in some observational studies [84, 86]. A prospective observational Brazilian study of 39 patients that received methylprednisolone 1 g/day bolus for 3 days every 3–4 months (also physical therapy and antispastic drugs in some of them) showed a 24.5% improvement from baseline in the Incapacity Status Scale after 2.2 years mean follow-up. This benefit showed to be significant until the third set of infusion [85]. A randomized, double-blind, placebo-controlled study of six months combination therapy between zidovudine and lamivudine in 16 patients, showed no significant changes in pain, bladder function, disability score, gait, proviral load or markers of T-cell activation or proliferation between the two arms at 48 weeks of follow-up [87]. Interferon alpha (IFN-α) was probed in a randomized, double-blind, multicenter, multidose trial of 48 patients. In a total follow-up of 8 weeks, 3.0 MU of IFN-α for 4 weeks was significantly better than 0.3 MU (but not than 1.0 MU) for improvement of motor dysfunction, urinary disturbances, and changes of neurologic signs without a difference in symptomatic side effects [88]. In a recent uncontrolled, phase 1–2a study of Mogamulizumab (an anti CCR4 monoclonal antibody), 21 patients received different doses of the drug with promising results in the decrease of proviral load, CSF inflammatory markers, spasticity, and motor disability [42]. Other therapies such as methotrexate, azathioprine, cyclosporine A, IFN-β, pentoxifylline, danazol, valproic acid, IL-2 receptor antagonist, and plasmapheresis have been tried in open trials and case series with disparate results [7, 84, 89–93].

Consequences of HAM/TSP

Overall, a patient with HAM/TSP lives 15 years less than the general population. The motor disturbances make necessary the use of a walking aid in the first decade since the onset of disease and the use of a wheelchair at 21 years of evolution on average [73]. The most affected areas of functionality in HAM/TSP patients, using the Functional Independence Measure (FIM) score, are the locomotion (walking and stairs) and bladder management items [94]. The bladder issues make the patients prone to urinary infections, urinary obstruction, social discomfort, sleep and mood disturbances and low quality of life [6, 7, 95–97]. Chronic lumbar and lower limb pain is also a concern, with a prevalence of 90% in HAM/TSP patients [98].

Infective Dermatitis Associated with HTLV-1 (IDH)

The first description of IDH was made in Jamaica in 1966, but then it was also reported in other prevalent areas of HTLV-1 infection such as other Caribbean isles, Japan and Brazil [99–102]. The onset of IDH occurs in childhood with an average age of 2 years and a tendency to improve into adulthood; a third of the cases can initiate at the first year of life [102, 103]. Also, there is a slight predominance in females (60%) [6]. Some risk factors associated with IDH are the presence of HLA class II haplotype DRB1∗DQB1∗ (1101-0301) and an elevated proviral load [104, 105]. The presence of IDH in childhood has been linked to later development of ATTL or HAM/TSP [26, 106, 107]. A Brazilian study showed that 44% of 74 patients with ATTL had dermatitis suggestive of IDH during childhood [108] and another study in the same country demonstrated 30% of the occurrence of HAM/TSP in 20 patients with a history of IDH [107].

In skin biopsies of patients with IDH, there is an important proliferation of CD4+ and CD8+ lymphocytes with an elevated CD4+/CD8+ ratio; also infiltration of non-activated CD8+ CTLs is another finding [26, 101, 109]. There are large quantities of IFN-γ produced by CD57+ cells in dermis and epidermis of patients with IDH [110]. *Staphylococcus aureus* and/or β-*hemolytic Streptococcus* superinfection is common in IDH and the stimulation of T cells due to antigens of these bacteria could offer a larger amount of cells for HTLV-1 replication [6, 26]. The histopathology shows chronic dermatitis that can mimic mycosis fungoides [111]. A mild to moderate epidermal and dermal lymphocytic infiltrate suggest an active immune response to HTLV-1 [111].

The clinical features of IDH consist of a severe exudative dermatitis with scaling or crusting of the scalp, forehead, eyelids, paranasal area, neck, retroauricular areas, external ear, axillae, or groin. Other common findings are a chronic watery nasal discharge, crusts in the anterior nares, blepharoconjunctivitis, lymphadenopathy and a generalized papular rash [26, 100]. As mentioned above superinfection with gram-positive cocci is habitual.

There are three major important items that must be present for the diagnosis of IDH: dermatitis of ≥2 sites, chronic watery rhinorrhea, and HTLV-1 seropositivity. Besides the aforementioned, early childhood onset and/or the good response of dermatitis with the use of antibiotics with a quick recurrence upon withdrawal are needed to meet the diagnostic criteria for IDH [100].

The treatment of IDH is based on long term use of antibiotic therapy, with a tendency to relapse at withdrawal. Continuous prophylactic therapy could be used. Also, the use of topical antibiotics or emollients can be useful. For pruritus, topical CS or antihistamines are indicated [26, 102].

Uveitis Associated with HTLV-1 (UAH) and Other Ocular Manifestations

The first report of uveitis associated with HTLV-1 (UAH) was made in Japan in 1989 [112]. UAH has been associated with the presence of HAM/TSP and autoimmune hyperthyroidism; interestingly HTLV-1 carriers under treatment for autoimmune hyperthyroidism may be prone to the development of UAH [113]. CD4+ TLs infected by HTLV-1 virus get into the aqueous humor with a higher proviral load than PBMC's; the mechanisms that explain how these infected lymphocytes get into this immune-privileged zone are not elucidated. These cells produce large amounts of IL-2, IL-6, IFN-γ, and TNF alpha as well as other cytokines that provoke intraocular inflammation [114, 115].

UAH is more common in females than males in a 3.5:1 ratio, especially women under 50 years old and is unilateral in 60%. The most important symptoms are "foggy" vision, ocular floaters, blurring of vision, ocular hyperemia, ocular pain, and photophobia. The most common type of presentation is panuveitis (49.6%) with moderate to severe vitreous opacities and mild anterior uveitis and retinal vasculitis, followed by intermediate uveitis (28.9%) [114]. The treatment of UAH consists of the use of topical/systemic CS and mydriatics. Relapsing is common [116]. The most important consequences are cataract and glaucoma [114].

Keratoconjunctivitis sicca and interstitial keratopathy have been related to patients with HAM/TSP. The latter manifestation was associated in a third of cases with uveitis and without response to local CS therapy [116].

Arthritis Associated with HTLV-1

The first reports that linked an inflammatory arthropathy with HTLV-1 virus came from ATTL and HAM/TSP patients [117, 118]. Arthritis associated with HTLV-1 is a chronic inflammatory arthropathy which is indistinguishable from Rheumatoid arthritis (RA) [119]. The most common joints affected are from hands and knees, and rheumatoid factor or antinuclear antibodies can be positive [120]. Interestingly, a Japanese study made in Nagasaki with 113 female patients diagnosed as RA found that in 13.2% (95% CI 5.1–21.2) of those patients, the disease was attributable to HTLV-1 infection, without clinical or laboratory differences between HTLV-I–infected and HTLV-I–uninfected RA patients [121]. Another prospective study from the United States showed an elevated incidence of arthritis in blood donors infected with HTLV-1 or HTLV-2 [122].

The clues that associate the presence of arthritis in HTLV-1 infected patients are the following: (1) Atypical lymphocytes (as ATTL like cells) have been observed in synovial fluid and synoviocytes of HTLV-1 infected patients

[123, 124]. (2) HTLV-1 proviral DNA has been found in the DNA of synovial fluid cells and synovial tissue cells [123]. (3) The presence of Tax mRNA and protein in synovial stromal cells [125]. (4) HTLV-1 has tropism for synovial cells *in vitro* [126]. (5) Higher proviral load in blood and synovium have been observed in patients who develop arthropathy versus asymptomatic patients, but similar to HAM/TSP patients. A possible mechanism of development of the arthritis is that T lymphocytes get into synovial space in response to HTLV-1, which is synovial cell tropic [6, 127].

There is no consensus in the treatment of arthritis associated with HTLV-1, with CS commonly used [6]. Also, anti-TNF agents seem to be less effective in HTLV-1 positive patients with RA [128]. More studies are needed to evaluate the use of DMARDS or biological therapy.

Sjögren's Syndrome Associated with HTLV-1 (SSAH)

A study made in Nagasaki, Japan, showed that 13% of 36 patients with primary Sjögren's syndrome (SS) were positive for HTLV-1. No difference was seen in xerostomia, xerophthalmia, enlargement of parotid glands, photosensitivity or Raynaud's phenomenon between patients with SS with or without antibodies to HTLV-1; but extra-glandular manifestations such as uveitis, myopathy, or recurrent fever were more frequent in the group of HTLV-1 positive patients [129]. Another report from Nagasaki found that in 135 patients with primary SS and 97 patients with secondary SS, 25% and 29.2% of them had anti-HTLV-1 antibodies, respectively. Also, there were no differences in the presence of Antinuclear (ANA), anti-Ro or anti-La antibodies between SS patients with or without seropositive for HTLV-1 [130]. Also, another Japanese study demonstrated that salivary IgA antibodies to HTLV-1 were common among seropositive patients with Sjögren's syndrome compared to patients with HAM/TSP or asymptomatic carriers [131]. There is no specific management for SSAH.

Inflammatory Myopathy Associated with HTLV-1 (IMAH)

The presence of HTLV-1 has been linked to polydermatomyositis (PM) [132, 133], inclusion body myositis (IBM) [134, 135], and dermatomyositis (DM) to a lesser degree [136]. Some studies have shown an increased seroprevalence of HTLV-1 in PM and IBM patients compared to controls [132, 134]. HTLV-1 has demonstrated to be myotoxic *in vitro* [137] and CD4+ TLs infected by HTLV-1 virus infiltrate the muscle tissue with no evidence myocyte infection [138]; CD8+ CTLs directed to Tax protein have been found in muscles of patients positive for HTLV-1 [133, 139] and anti-Tax cytotoxic T cells are chronically recruited within inflamed tissues of patients with IMAH [139]. A Jamaican retrospective study of 38 patients with polymyositis, of whom 24 were seropositive for HTLV-1, showed that the latter had a longer time between the onset of symptoms and diagnosis, more frequent admissions to hospital and lesser chest pain, dyspnea or joint swelling than the seronegative. No difference was seen for ANA, creatine kinase, or anti-Jo-1 antibodies [132]. IMAH can be resistant to CS or other immunosuppressants [6].

Pulmonary Manifestations of HTLV-1 Infection (PMH)

Concerns about pulmonary manifestations of HTLV-1 infection began with cases of HAM/TSP patients that developed pulmonary lymphocytic inflammatory infiltrates [140, 141] and morphologic changes of the lungs in CT scan [142, 143]. A Japanese retrospective study found that 30.1% of 320 patients with HTLV-1 had pulmonary findings on CT scans. The abnormalities were consistent with centrilobular nodules (97%), thickening of bronchovascular bundles (56%), ground-glass opacity (52%), bronchiectasis (51%), interlobular septal thickening (29%), and consolidation (5%). Of them, 58 patients had a lung biopsy: a lymphocytic infiltration along respiratory bronchioles and bronchovascular bundles was the most prevalent finding [144]. The pulmonary manifestations of HTLV-1 infection are different between patients with ATTL and the presence of HAM/TSP or asymptomatic carriers (Table 16.2). Most patients with PMH are asymptomatic [6]. There is no specific treatment but unresponsiveness of long courses of CS has been described [142].

In patients with pulmonary disease and infection with HTLV-1, there are an increased number of T lymphocytes (CD4+ and CD 25+) in bronchoalveolar lavage fluid (BAFL) and a Th1 immune response with augmented production of IL-2R, IL-2, IL-12, and IFN-γ [146]. The degree of HTLV-1 proviral load in BALF is related to the number of lymphocytes in it [147]. In response to Tax protein, there are also elevated levels of MIP-1α and ICAM -1 which are implicated in activation and recruitment of inflammatory cells and high levels of IP-10, an important mediator in pulmonary fibrosis

Table 16.2 Pulmonary manifestations of HTLV-1 infection [145]

ATTL patients	Opportunistic infections: Pneumocystis, strongyloidiasis, tuberculosis Pulmonary leukemic infiltrates
HAM/TSP or asymptomatic patients	T lymphocytic alveolitis Interstitial pneumonia Bronchiolitis and diffuse panbronchiolitis Infections: Pulmonary cryptococcosis, tuberculosis, and community-acquired pneumonia

[148]. Also, a direct relationship exists between *Foxp3* and *HBZ* mRNA and the number of lymphocytes in BAFL of patients with lung manifestations in the context of HTLV-1 infection [146]. Interestingly, a higher number of CD8+ CTLs in BAFL than peripheral blood have been observed in patients infected with HTLV-1, a finding that could imply a selective infiltration in the lung in response to the virus [141, 149].

Some data suggest that proviral load and HTLV-1 serotype could impact in prognosis. A prospective cohort study of 840 indigenous Australian adults showed that a higher baseline HTVL-1c serotype proviral load (HTLV-1c pVL) in peripheral blood leukocytes was linked to higher mortality due to bronchiectasis-related events. HTLV-1c pVL was also associated with higher airway inflammation [150]. There is a frequent co-infection of HTLV-1 and tuberculosis (TB) with increased mortality, need for hospitalization, or probability of treatment for pulmonary TB [145, 151–153]. The higher susceptibility to TB could be explained due to lesser production of TNF alpha, while the severity of the pulmonary TB may be related to an exaggerated inflammatory response in the context of HTLV-1 infection [151].

Other Associations

The relationship between systemic lupus erythematosus (SLE) and HTLV-1 infection is controversial [154–156]. While there are some case reports that support the association [157–159], an Iranian cross-sectional case-control study of 1045 patients (130 SLE patients and 915 healthy controls) showed that HTLV-1 was not a predictor factor for SLE [154]. Another study suggests that SLE patients who are seropositive for HTLV-1 have an older age at onset of the disease, a higher lymphocyte count, and need for lower doses of CS for maintenance than seronegative patients [156]. There are four reported cases of mixed connective tissue disease in HTLV-1 carriers reported in the literature [160–163]. Tubulointerstitial nephritis (TIN) in Japanese HTLV-1 carriers have been associated with the presence of uveitis (TINU syndrome) in two patients and other patients with class I lupus nephritis [164, 165]. Some other cases of liver disease have been published (including autoimmune hepatitis and primary biliary cirrhosis) [6, 166]. Autoimmune thyroid diseases have been related to HTLV-1 [167, 168]; there are reports that link Hashimoto's disease with HAM/TSP and Basedow-Graves with uveitis [6, 169].

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Other Viral Arthritides

17

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Introduction

The list of viruses associated with arthritis is extensive. Most viral arthritides are acute and self-limiting; therefore, their recognition is very important to distinguish them from more debilitating and chronic diseases such as systemic autoimmune or connective tissue diseases. Some of them have been described in previous chapters (Table 17.1).

Table 17.1 Viruses that cause arthritis

Hepatitis: A, B, C	Mumps
HIV, HTLV-1	Dengue
Parvovirus	Adenovirus
Alphavirus (Togaviridae): Chikungunya, Ross river virus, O'nyong-nyong, Barmah Forest virus, Sindbis virus, Mayaro	Herpes: Varicella, Epstein-Barr, Herpes simplex, Cytomegalovirus.
Ebola	Enterovirus: Coxsackie, ECHO virus
Rubella	

Rubella Arthritis

Rubella virus is a RNA virus, belonging to the rubivirus (RV) genus of the Togaviridae family. RV is the causal agent of rubella, also known as German measles, three-day measles. The transmission mode occurs by inhalation of airborne droplets or from mother to fetus. This infectious disease affects predominantly children and generally is a mild and self-limited disorder and is characterized by low-grade fever, sore throat, and lymphadenopathy, which appears before rash that starts on the face and spreads to the rest of the body. Rubella can cause a miscarriage or serious birth defects in a developing baby if a woman is infected while she is pregnant. Serious birth defects can occur and include ocular, auditory, central nervous system and cardiac problems. The diagnosis of rubella cannot be made on clinical grounds alone because other viral agents can induce a similar illness. Laboratory tests are needed to confirm the diagnosis. Serologic tests are used in both acute and convalescent stages. RT-PCR test is most sensitivity for diagnosis of rubella [1–3]. Inflammatory musculoskeletal involvement can manifest following infection or after vaccination.

Rubella Arthritis Following Natural Infection

It affects adults more than children, and the incidence of arthritis in adults with rubella infection varies from 15% to 61% [4–6]. This disease affects young adult females (52%) more than males (8.7%) [4–9]. Chronologically the onset of arthritis develops following the rubella rash, but arthritis may antedate or postdate the rash by 6 and 4 days, respectively [8]. The clinical pattern is usually an additive symmetrical polyarthritis, but sometimes is migratory. Joints most commonly involved are the small joints of the hand and knees [9]. The duration of arthritis varies from 1 day [10] to 7 weeks [11]. Arthralgia or joint stiffness may persist for longer periods of time [4, 8, 11]. Other clinical manifestations reported are carpal tunnel syndrome [4, 6, 8, 9] and tenosynovitis of the extensor tendon sheaths of the hands [8, 12]. The synovial fluid obtained from patients is inflammatory type [9]. Only one report of isolation of rubella virus from synovial fluid has been described [13].

Post-vaccination Rubella Arthritis

The association between rubella in pregnancy and congenital anomalies emphasizes the need of developing a vaccine to prevent infection in pregnancy and thus the birth of babies with rubella-induced congenital defects [14].

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_17

The vaccine against rubella is live attenuated virus (Table 17.2). All virus strains used in rubella vaccine manufacture have an arthritogenic potential and induce various degrees of inflammatory joint involvement [15]. Arthralgia and arthritis following vaccination have been described since the earliest studies of rubella vaccines [14–17]. The arthritis that follows vaccination with attenuated live rubella is indistinguishable from that following natural rubella infection.

Relationship of Acute Joint Involvement to Age and Sex

Arthritis following vaccination of pre-pubertal children is uncommon. In contrast to adults, sex had no influence on the incidence of joint symptom in children [18, 19]. Joint symptoms usually begin after the second week and peak between the 32nd and the 38th post-vaccination day [19, 20]. There is an association between joint involvement and increasing age [21, 22], which was shown by Swartz et al. who conducted a study in 159 women who were administered HPV-77-DES and observed no articular symptoms in children younger than 13 years of age and articular symptoms in 50% of patients between 25 and 33 years of age [21].

The frequency or intensity of articular symptoms depends on the pre-vaccination immunologic status of the children. On the basis of rubella hemagglutination-inhibition (HAI), those who do not have rubella antibody or a titer less than 1.4 (susceptible group), the majority (80%) reported to have joint complaints compared with the immune group (titers higher than 1.4 HAI) who experienced mild symptoms and arthralgia and not arthritis [20]. Tingle et al. conducted a study to compare joint manifestations during a prospective RA 27/3 rubella immunization trial and during an intercurrent wild rubella epidemic and found that wild rubella infection in adult populations is associated with a higher incidence, increased severity, and more prolonged duration of joint manifestations than is seen after rubella immunization [23, 24].

Singh et al. conducted a study to determine the role of circulating immune complex (CIC) in the pathogenesis of rubella-associated arthritis or arthralgia but did not find data to support the direct role for raised CIC levels [25].

Table 17.2 Rubella vaccines

Vaccine	Culture
HPV-77-DK 12 strain	Dog kidney cell
HPV-77 DEV 5 strain	Duck embryo cell
Cendehill 51 strain	Rabbit kidney cell
RA 27/3 strain	Human diploid cell

Relationship of Acute Joint Manifestations to Vaccination

Rates of acute arthralgia and arthritis following rubella immunization differ by vaccine strain, with the HPV-77 (DK) variant producing the most joint manifestations in all age groups [17, 19, 26]. The HPV-77 (DEV) and RA 27/3 strains have also been observed to induce joint symptoms, but the symptoms are more similar to the reaction following natural disease, and the arthropathy is more likely to occur in adults than in children [21, 22, 27, 28] (Table 17.3).

Persistent or recurrent arthritis may be a sequel of attenuated live rubella virus vaccination, a complication seldom described after natural rubella infection [24, 29–34]. RV has been recovered from synovial fluid following rubella immunization in a patient with arthritis post vaccination [28].

Other post-rubella vaccine pain syndromes described in children are the so-called “arm and leg syndrome” and the “catcher’s crouch” syndrome. In the first case patients describe nocturnal hand and wrist pain, often associated with digital paresthesia. While in the second situation, patients describe popliteal fossa pain, bilateral, causing the children to walk with knees flexed, in a crouching position.

Association of RV with Systemic Connective Tissue Disease

It has long been suspected that rubella virus infection might be linked to chronic inflammatory joint disease. The widespread use of rubella vaccines and reports suggesting that RV is associated with chronic inflammatory joint disease has generated considerable public concern. Grahame et al. reported isolation of live rubella virus from synovial fluid obtained from six cases of chronic inflammatory articular disease. None of the patients assessed had the presentation typical of rubella arthritis, and none would have been suspected of suffering rubella [35]. Chantler et al. also reported the isolation of rubella virus from peripheral blood and synovial fluid mononuclear cells in 35% of patients with chronic inflammatory articular disease not associated with recent

Table 17.3 Frequency of joint symptoms in adult females following administration of rubella strains

	Proportion(%) of adult females developing acute arthritis or arthralgia	
Vaccine	Pooled proportion	95% Confidence interval
HPV-77(DK)	49	35–66
HPV-77 (DEV)	30	27–33
Cendehill	9	08–10
RA 27/3	14	13–15

infection or immunization with rubella virus [36]. Using culture and PCR technique Rubella virus (RV) has been isolated from joint aspirates following natural infection and vaccination in a few patients. This hypothesis generated considerable public concern. Bosma et al. conducted a study in adults and children with various chronic inflammatory joint disease and tested synovial fluid (SF), SF cells (SFCs), and synovial biopsies for RV by using both a sensitive reverse transcription-nested PCR (RT-PCR) and a well-established RV isolation technique but did not find evidence of RV in 30 synovial biopsies [37].

Therapy

In view of the self-limited nature, therapy should be conservative. Non-steroidal anti-inflammatory drugs or short courses of glucocorticoids have been used and reported to be of benefit [20].

Adenovirus Arthritis

Human adenoviruses (HAdV) are a DNA virus belonging to the Mastadenovirus genus in the family Adenoviridae; seven subgroups (A-G) and 68 serotypes are known to cause human infection. Adenoviruses are characterized by their ubiquity and persistence in host tissues for long periods of time. They may induce infection without disease (asymptomatic infection), and only about 45% of adenovirus infections result in disease (virus has been recovered from tonsils or adenoids from healthy children). The group name is due to its discovery in many adenoid tissue specimens [1, 2].

Depending on the serotype, they can also cause clinical syndromes such as childhood febrile illness; pharyngoconjunctival fever associated with adenovirus types 1, 2, 3, 5, 7, 7a, and 21; epidemic keratoconjunctivitis associated with serotypes 3, 8, 9, 19, and 37; acute respiratory disease most often associated with adenovirus types 1, 2, 3, 5, 7, 7a, 7b, 14a, and 21 (four in military recruits); acute hemorrhagic cystitis and interstitial nephritis associated with 11, 34, and 35; and acute gastroenteritis associated with subtypes 40 and 41 [1, 2, 38].

Infection is usually transmitted in droplets of respiratory or ocular secretions. The transmission mode occurs by touching an object or part of the body with adenovirus on it and then self-touching mouth, nose, and eyes.

This disease can occur in immunocompetent and immunosuppressed individuals. Symptoms associated with HAdV infection include fever, acute respiratory illness, gastroenteritis, and conjunctivitis. HAdV infection can be severe, particularly among immunocompromised patients, and can cause respiratory failure, disseminated infection, hemorrhagic cystitis, neurologic disease, and death [38, 39]. Outbreaks of HAdV have been reported globally in communities [40] and in closed or crowded settings, including dormitories, health care settings, and among military recruits [41, 42].

Inflammatory joint involvement associated with HAdV can appear after the onset of upper respiratory tract symptoms or after the immunization with a vaccine to adenovirus. These manifestations follow an acute course, and the usual articular pattern is polyarthritis accompanied by erythematous rash. Diagnosis of reported cases can be made with a raise of type-specific antibodies to adenovirus type 7 and positive throat cultures for the virus [43, 44]. Meyer-Bahlburg et al. reported a patient with Cernunnos immunodeficiency with chronic monoarthritis associated to adenovirus [45].

Diagnosis

HAdV can be detected in any affected sites (e.g., nasopharyngeal aspirates, swabs, washings, bronchoalveolar lavage, urine, stool, blood, synovial fluid). Serologic testing of acute and convalescent sera may be necessary to confirm the relationship between the virus and the observed clinical picture [1].

The direct fluorescent assay (DFA) helps to diagnose HAd infection. Any type of sample including peripheral blood, stool, urine, bronchoalveolar fluid, nasopharyngeal aspirates, or swabs can be used for diagnostic testing. Its disadvantage is low sensitivity (70–95%). Results are obtained within 10–60 minutes. Shetty et al. conducted a study and found that the DFA was practical and comparable with conventional cell culture [46].

Culture

Cultures remain the gold standard for any viral infection. It usually requires a minimum of 2–10 days to provide useful information.

PCR

PCR-based techniques are rapid and more reliable. PCR-based assays have been established as a standard diagnostic tool for rapid, specific, quantitative, and highly sensitive detection of HAdV in any diagnostic material [47–49]. Quantification of the viral load using real-time PCR is a useful marker to assess response to therapy [50–52].

Epstein-Barr Arthritis

Epstein-Barr virus (EBV) also called human herpesvirus 4(HHV-4) is a DNA virus belonging to the Lymphocryptovirus genus of the Herpesviridae family. EBV is the causal agent of infectious mononucleosis (also known as mono or glandular fever). EBV is ubiquitous, and a great percentage of adults have antibodies against it. The transmission mode of EBV most commonly is through bodily fluids, especially saliva. However, EBV can also spread through blood and semen during sexual contact, blood transfusions, and organ transplantations. EBV can be spread by using objects, such as a toothbrush or drinking glass that an infected person has recently used. The acute infection usually is asymptomatic in children, but 30–50% of immunocompetent adolescent and adult develop infectious mononucleosis. The symptoms include fever, fatigue, sore throat, heat and body pain, swollen lymph nodes, enlarged liver and spleen, and rash. EBV is also associated with lymphoproliferative disorders, Burkitt's lymphoma, and nasopharyngeal carcinoma [1, 2, 53].

Inflammatory joint involvement associated with infectious mononucleosis has been rarely reported [54]. Arthralgia may occur in approximately 5–10% of patients [55]. The joint involvement can manifest with different clinical patterns, such as monoarthritis [56–58], oligoarthritis [59, 60], and additive, symmetric polyarthritis [60–62]. All clinical syndromes are acute in their presentation. The diagnosis is made using serologic tests such as IgM and IgG viral capsid antigen (VCA) antibodies, anti-EB nuclear antigen (EBNA) and early antigen (EA-R), heterophile antibody, and atypical lymphocytosis. However, it should be mentioned cases of infectious mononucleosis and articular involvement and negative heterophile antibody [58, 62] and absence of atypical lymphocytosis [61] have been described. In the cases where synovial fluid was obtained, these were of inflammatory type.

Symptomatic EBV patients exhibit very good clinical response to nonsteroidal anti-inflammatory agents. Glucocorticoids have been given to some patients because of the severity of their disease and extensive organ system involvement [60, 61].

Diagnosis

Laboratory investigations used to diagnose EBV infectious are various. Besides leukocytosis, lymphocytosis with atypical lymphocytes, and abnormalities of affected organs, there are tests for detecting non-specific heterophile antibodies and specific anti-EBV antibodies, as well as molecular technology used to detect EBV DNA (Table 17.4).

Table 17.4 Laboratory tests for diagnosis of EBV infection

Test	Advantages	Disadvantages
Heterophile antibodies	Can distinguish acute from past infection, inexpensive, and simple	Not very sensitive (sensitivity 85%)
Anti-EA(D) IgG	Of some value in distinguishing acute from past infection; inexpensive	Not useful in at least 10% of cases
EBV IgG immunoblotting	Can distinguish acute from past infection	Individual antibody production; expensive
IgG avidity	Can distinguish acute from past infection	Individual maturation. Not useful in newborns (maternal antibodies)
Molecular technique (PCR)	Can distinguish acute from past infection	Poor conservation of blood sample, presence of nucleasis; expensive, specialized training required

Role of Epstein-Barr Virus in the Etiology of Autoimmune Disease

It has long been suspected that EBV may be linked to the development of autoimmune inflammatory diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, and rheumatoid arthritis. Development of autoimmune diseases will depend on multiple factors including individual immunological profile, which is genetically determined, individual combinations of infection, and environmentally induced immunomodulation (i.e., ultraviolet light). In the case of SLE, numerous studies have described higher frequencies and elevated titers of EBV-antibody (IgM, IgG, and IgA) against antigens in SLE patients compared with healthy controls [63–67]. Hanlonl et al. carried out a meta-analysis and found evidences in support of the notion that infection with EBV predisposes to the development of SLE [68]. In relation to Sjögren's syndrome, it was revealed the presence of EBV-infected cells in specific lymphoid structures in the salivary glands of Sjögren's syndrome patients [69]. It has also been shown an increased positivity of anti-early antigen IgG, which correlated with the presence of anti-SSA and anti-SSB [70]. Erre et al. showed increased EBV DNA positivity in PBMCs in 79.2% of RA patients compared with 56.9% of healthy controls. Furthermore, they found an increased prevalence in RA patients of both EBNA1 IgG (90% compared with 69% of healthy controls) and EBV-early antigen IgG (37% compared with 10.3% of healthy controls) [71]. However, Ball et al. carried out a meta-analysis and did not find any evidence demonstrating an association between EBV seroprevalence and RA, and therefore their date does not support the hypothesis that prior infection with EBV predisposes to the development of RA [72]. This contrasts with meta-analyses that indicate EBV infection is associated with RA and SLE.

Harley et al., supported by NIH's National Institute of Allergy and Infectious Diseases (NIAID) and several other NIH components, have conducted a study and found a protein produced by the virus—EBNA2—recruits human proteins called transcription factors to bind to regions of both the EBV genome and the cell's own genome. EBNA2 and its related transcription factors activate some of the human genes associated with the risk for systemic lupus erythematosus and several other autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis, and celiac disease [73].

Varicella-Zoster Arthritis

Varicella-zoster virus (VZV) , also called chickenpox virus, varicella virus, zoster virus, and human herpesvirus type 3 HHV-3, is a DNA virus belonging to the Varicellovirus genus of the Herpesviridae family. VZV is the causal agent of chickenpox (also known as varicella).

The mode of transmission of varicella is by direct contact (touching the rash), droplet, or airborne spread (coughing and sneezing) of vesicle fluid or secretions of the respiratory tract of cases or of vesicle fluid of patients with herpes zoster. The mode of transmission indirectly is through articles freshly soiled by discharge viral particles. Clinical picture is characterized by fever, tiredness, and weakness, followed by itchy, vesicular rash, usually starting on the scalp and face and then spreading to the rest of the body. Rash usually begins as small lumps that turn into blisters and will dry, crust over, and eventually form scabs. Vesicles are more abundant on covered than the exposed parts of the body. Lesions tend to appear more abundant on covered than on exposed parts of the body.

Inflammatory joint involvement associated with varicella is uncommon. The articular pattern predominantly is monoarthritis, and the joint most affected is the knee, followed by polyarthritis, which tends to be additive [74–78]. The majority of cases reported appeared after the onset of the varicella exanthem; however, there are cases reported before the onset of skin involvement [79]. Synovial fluid is inflammatory type. No positive viral culture has been reported. Diagnosis is made using PCR in synovial fluid [80–82]. Arthritis resolves completely in a few days on nonsteroidal anti-inflammatory agents. All symptoms and signs of arthritis resolve after 1 month [79].

Mumps Virus

Mumps virus (MV) is the etiologic agent of mumps. MV is a RNA virus belonging to the genus Rubulavirus in the family Paramyxoviridae. The virus is transmitted by direct contact, droplet spread, or contaminated objects, that is, coughing, sneezing, or talking, sharing items with others, and touching objects or surfaces with unwashed hands that are then touched by others. The symptoms include fever, headache, malaise, tiredness, muscle aches, and parotitis [1, 2].

Diagnosis

Serology testing with a positive IgM suggests recent infection while IgG positivity will persist lifelong. Virus culture is the gold standard; this virus can be detected or isolated from the saliva, pharynx, the cerebrospinal fluid, and synovial fluid. The PCR technique permits a rapid diagnosis of this virus.

Inflammatory joint involvement associated to mumps is uncommon and infrequently reported in the medical literature. Mumps arthritis follows the onset of parotitis by a mean of 1–2 weeks [83], but Solem reported a patient with migrating polyarthritis without parotitis and positive mumps complement fixation test with a significant titer increase [84]. Serologic studies suggest that as many as 30% of mumps virus infections are subclinical [85]. It has been described three clinical forms of joint involvement and these developing between 1 and 3 weeks following parotitis [84, 86]:

1. Arthralgia without clinical signs of inflammation.
2. Frank arthritis, polyarticular and often migratory commonly affecting large joints: shoulder, knee, ankle, and less frequently small joints are involved.
3. Monoarticular arthritis most frequently affecting knees, hips, and ankles.

During the course of arthritis, other systemic complaints including fever generally of low grade can be present. Diagnosis has been made after rise of mumps antibody titer in joint fluids and serum. Of the cases reported in the literature, the mumps virus has yet to be isolated from synovial tissue.

Therapy with salicylates has not been effective, but the use of glucocorticoids provides improvement of articular symptomatology [83]. The course of the arthritis is unaltered by therapy, and the duration of the arthritis is unpredictable, but a two-week course of oral prednisone or non-anti-inflammatory agents is recommended [86].

Enteroviruses Arthritis

The virus is a RNA virus belonging to the genus enterovirus in the family picornavirus. There are many serotypes of enterovirus (> 100) but four main species grouped on genetic sequencing (A-D). Clinicians may use older biological cat-

egorization. The enterovirus comprises several subgroups of which the following may cause disease in humans: polioviruses (type 1–3), coxsackieviruses group A (types 1–22, 24) and B (types 1–6), Echoviruses (types 1–9, 11–27), and newer enteroviruses (types 29–34, 68–72). The human enterovirus 72 is hepatitis A virus. The mode of transmission is from person to person mainly by the fecal-oral route, and to a lesser degree by the respiratory route. Some types associated with conjunctivitis spread by direct contact. The enteroviruses have a worldwide distribution, and more than 90% of infections caused by Coxsackie and echovirus are asymptomatic [1, 2, 87, 88]. The symptoms include fever, rash, herpangina, hand, foot and mouth disease, epidemic myalgia, pleurodynia, myocarditis, pericarditis, and conjunctivitis [1, 2, 87, 88] (Table 17.5).

Diagnosis of Enteroviruses

At present, the polymerase chain reaction (PCR) with reverse transcription and complementary DNA amplification (RT-PCR) is being increasingly used to detect enteroviral infection in tissue and body fluids. This technique has allowed an improvement in diagnostic sensitivity and speed. Another diagnostic method is the detection of increased neutralizing antibody titer changes between paired acute and convalescent serum samples. However, this method is often expensive and cumbersome, requiring careful selection of serotypes for use in antigens. The true frequency of joint involvement associated to enterovirus is unknown, and the literature published about this association is scarce.

Coxsackievirus: The few cases reported are acute manifestations such as polyarthralgia or polyarthritis associated with systemic symptoms fever, pleuritis, myopericarditis, and viral antibody titers increased for Coxsackie B2, B3, B4, and A9. It is not known whether the infection of joints by virus is reactive or direct because virus has not been isolated [89, 90].

Table 17.5 Clinical syndromes associated with enteroviruses infection. (Enteroviruses: Coxsackie and ECHO Virus)

Syndrome	Occurrence	Coxsackie A	Coxsackie B	Echovirus
Asymptomatic	Frequent	+	+	+
Paralytic	Sporadic	+	+	+
Encephalitis, meningitis	Outbreaks	+	+	+
Carditis	Sporadic	+	+	+
Neonatal disease	Outbreaks		+	+
Hand foot mouth	Common	+		
Respiratory infections	Common	+	+	+

Echovirus: The few reported cases are acute manifestations. The patterns were monoarthritis and polyarthritis. Both cases were accompanied by fever. In the case of polyarthritis the diagnosis was made by isolation of echovirus 9 from throat and rectal swab specimens, although the rigorous diagnosis of echovirus infection requires isolation of the agent from the joint and demonstration of a rise in convalescent titers to neutralizing antibody. In the case of monoarthritis reported echovirus type 11 was isolated from the synovial fluid [91, 92].

Therapy: There is no specific treatment. Currently no antiviral medications are approved for the treatment of enterovirus infections.

Role of Enteroviruses in the Etiology of Autoimmune Disorders

A potential role of Coxsackievirus infection on the development of Sjögren's syndrome has been proposed. Triantafyllopoulou et al. found increased titer of antibodies against several coxsackievirus B serotypes in patients with Sjögren's syndrome compared with controls. Also, RT-PCR performed in biopsy of minor salivary gland of three patients gave positive results [93].

Cytomegalovirus Arthritis (CMV)

The CMV is a group of DNA viruses belonging to the genus cytomegalovirus in the family Herpesviridae. The species that infects human beings is also known as human herpesvirus 5 (HHV-5). CMV is ubiquitous. Approximately 50–70% of adults in developed countries developed antibody against CMV, and this percentage is higher in developing countries. The mode of transmission is through saliva, sexual contact, placental transfer, breastfeeding, blood transfusion, or solid-organ transplantation or hematopoietic stem-cell transplantation [1].

CMV infections occur more frequently in immunocompromised hosts. A mononucleosis syndrome similar to primary Epstein-Barr virus (EBV) infection can be caused by CMV infection, with persistent fever, myalgia, and cervical adenopathy. Unlike EBV-associated infectious mononucleosis, cytomegalovirus rarely causes tonsillopharyngitis or large splenomegaly [94]. Laboratory tests used to diagnose CMV are seroconversion, isolation of the virus from fluids and tissue, and PCR from body fluids and tissue [95, 96].

Inflammatory joint involvement associated with CMV infection is rare, and the medical literature about this association is scarce. There is a case reported in an immuno-

suppressed patient who developed acute monoarthritis. Diagnosis was made through isolation of virus from the synovial fluid; also electron microscopy revealed particles inside synovial fluid cells, morphologically consistent with CMV virions [97].

Role of Cytomegalovirus in the Etiology of Autoimmune Diseases

An etiologic link between CMV and systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis by some findings reported by the literature has been suggested, but currently the evidence does not convincingly support this notion [96, 97].

Herpes Simplex Arthritis (HSV)

HSV are DNA viruses (HSV-1and HSV2) belonging to the genus simplex virus in the family Herpesviridae. Inflammatory joint involvement in HSV is rare. The articular pattern described was monoarticular, and the joints most affected were lower extremity (knee or ankle or both). The articular disorder followed the appearance of herpetic lesions and lasted from 4 days to 4 months. The diagnosis was made with culture positive Herpesvirus hominis (herpes simplex) in the synovial fluid and an increased serum viral titer [98, 99].

The occurrence of viremia with HSV type 1 in both normal and immunosuppressed adults has been reported. One patient developed arthritis after the appearance of herpetic lesions by 3–4 days. The pattern was mono-oligoarthritis and lasted 7 days. The diagnosis was made by serologic tests [100].

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Part III

Arthritis Due to Mycobacteria, Fungi, Spirochete, and Miscellaneous Arthritides

Tuberculous and Nontuberculous Mycobacterial Infections

18

G. Omondi Oyoo and Eugene Kalman Genga

Introduction

Skeletal tuberculosis (TB) refers to TB affecting the bones and/or joints. It is an ancient disease that has been found in Egyptian mummies dating as far back as 9000 years [1]. Musculoskeletal involvement TB is rare and is seen in 1–3% of patients with TB [2]. About half of these cases affect the spine, and the rest are extraspinal osteoarticular joints [3, 4]. Poncet's disease or tubercular rheumatism presents during the acute TB infection as a nondestructive polyarthritis without evidence of direct mycobacterial involvement of the joints nor any other known cause of polyarthritis detected [5, 6]. It is a different entity from tuberculosis arthritis (TB arthritis). TB arthritis is usually monoarticular and in which the organism can be isolated from the joint [5]. This chapter discusses clinical issues related to skeletal TB and those due to nontuberculous mycobacteria.

Epidemiology

More than two billion people (about 30% of the world population) are estimated to be infected with M. tuberculosis [7]. The highest rates (100 per 100,000 or higher) are observed in sub-Saharan Africa, India, and the islands of Southeast Asia and Micronesia. The major contributors in these regions are poverty, human immunodeficiency virus (HIV), and drug resistance. About 95% of TB cases occur in developing countries. Approximately one in nine new TB cases occurs in individuals who are infected with HIV [7, 8], and especially in Africa which has a higher prevalence of HIV infection, data shows that up to one-third of adults with osteoarticular infections are HIV positive [7, 8]. Data from Europe and USA have shown an increase in extrapulmonary TB (EPTB) from 7.6% to 20–40%. This has been attributed to HIV. In developed countries, the majority (58–81%) of skeletal TB cases occur in immigrants [9].

Bone and joint TB shows a bimodal age distribution: In natives of developed countries, the disease commonly affects people older than 55 years, whereas in immigrants, it is more common in younger individuals (20–35 years old) [10–12]. Concomitant pulmonary and skeletal TB is diagnosed in 6.9–29% of cases [11, 12]. Pott's disease (a disease of the spine) is the most common form of skeletal TB comprising about half of musculoskeletal TB cases. This is followed by tuberculous arthritis and extraspinal tuberculous osteomyelitis, respectively [13].

Pathogenesis

Skeletal TB usually is a result of reactivation of bacilli lodged in bone during the original seeding of the primary infection. Progression of the disease happens in the background when local immune defenses fail, as in the setting of malnutrition, advancing age, HIV infection, or renal failure [14]. The bacillus tends to favor the spine and large joints due to the rich vascular supply of the vertebra and growth plates of the long bones. It is postulated that tuberculous arthritis is an extension of an initial infectious loci in the bone to the joint. Other sources of seeding include from the lungs via the lymphatic system, direct inoculation of mycobacteria following a traumatic injury, or during surgical procedures such as joint arthroplasty [15, 16].

In highly endemic regions, musculoskeletal TB usually manifests clinically in the year following primary lung infection and therefore occurs most frequently in relatively young patients. Outside endemic areas, musculoskeletal TB is more commonly associated with late reactivation of infection and occurs mainly in adults. TB-associated bone and joint involvement can either be the caseous exudative type or the granular type. The caseous exudative type is seen more

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_18

in children and is characterized by bone destruction, local swelling, abscess formation, sinus formation, and constitutional symptoms. The granular type is more in adults and is insidious and less destructive than the caseous exudative type, and abscess formation is less common [17, 18].

Clinical Manifestations

Virtually any bone can be infected with M. tuberculosis. Musculoskeletal TB can manifest in the following forms—spondylitis (Pott's disease), arthritis, and osteomyelitis.

Spondylitis (Pott's Disease)

The most commonly affected sites are the lower thoracic and upper lumbar region. It rarely manifests in the cervical and upper thoracic region. The initial site of infection is the anterior aspect of the intervertebral joints after which it spreads to the adjacent vertebral body. Once two adjacent vertebrae are involved, infection enters the adjoining intervertebral disc space. This leads to the death of the avascular disc tissue, vertebral narrowing, and collapse [19, 20]. This leads to a Gibbus deformity, a form of structural kyphosis that eventually distorts spinal canal anatomy. Paraplegia usually results from spinal cord compression due to gibbus or late onset due to paraplegia occurs due to osteophytes and other chronic degenerative changes at a site of prior infection. Formation of a "cold abscess" (soft tissue mass) at the site is common.

Usually the diagnosis of Pott's disease is delayed due to its low incidence and slow, subacute course. Commonly it presents with local pain which increases with severity over time associated with muscle spasm and rigidity [19, 20]. Some patients develop an erect posture with "aldermanic gait" in which the patient walks in short, deliberate steps to compensate for the pain around the infection site. In about 40–70% of the cases may present with symptoms and signs of cord compression at the time of diagnosis. Constitutional symptoms such as fever and weight loss are present in less than 40% of cases [19].

Arthritis

Tuberculous Arthritis

Tuberculous Arthritis is usually monoarticular and can affect any joint. The most commonly affected joint is the hip followed by the knee. It presents with a "cold joint" without any signs of an acute infection. It can also present with swelling, pain, and/or loss of joint function that progress over weeks to months. Constitutional symptoms, fever, and weight loss occur in only about 30% of cases. Some advanced cases manifest as discharging sinuses. Over time the joint undergoes progressive destruction, disorganization of its architecture with joint deformity. Histopathology reveals granulomatous changes with synovial proliferation with joint effusion and erosion of cartilage [21, 22]. There are five stages of TB arthritis [23, 24]. Stage 1 manifests as soft tissue swelling, localized osteoporosis and has good outcomes on treatment. Stage 2 has early arthritis with bone erosions; treatment is good but leaves behind joint stiffness. Stage 3 Stage has advanced arthritis with subperichondral cyst and loss of joint space. This complicates after treatment with loss of joint motion and flexibility. Stage 4 has advanced arthritis with joint destruction and no motion at the joint after treatment. Stage 5 is ankylosis of joint [23, 24].

Poncet's Disease

Poncet's disease is an acute symmetrical polyarthritis involving large and small joints associated with active extrapulmonary, pulmonary, or miliary TB but no evidence of active TB [25, 26]. It's a rare entity of unknown pathogenesis thought to be immune mediated. HIV has been identified as a risk factor. Generally, it resolves within a few weeks of start of TB treatment. It leaves no residual joint destruction [25, 26].

Diagnosis

Diagnosis of skeletal tuberculosis (TB) is a challenge especially considering that in more than half the cases there is no evidence of active chest disease. The indolent nature of the disease also contributes to its delays. Clues from history including prior TB contact, the systemic B-symptoms of TB, and countries of origin of the patient can help raise the level of suspicion for TB. The diagnosis of musculoskeletal TB is established by microscopy and culture of infected material.

Bacteriology

The gold standard for diagnosis of tuberculosis is demonstration of acid fast bacillus from any body tissue or fluid [27]. Tissue may be obtained by needle aspiration and/or biopsy. CT guidance is useful in regions where available. Tuberculous arthritis can be diagnosed from a synovial biopsy. The findings can be non-specific but raised or low white cell count with predominantly neutrophils or lymphocytes is suggestive [27–29]. Cases of draining sinuses culture of this material may be collected for culture. Examples of culture methods available include Lowenstein-Jensen medium, radiometric (Bactec 12B liquid medium), and non-radiometric (Bactec MGIT 960 system) [27]. The major drawback is the long length required to grow the culture. There are newer rapid automated growth systems and nucleic acid detection methods that have been limited in use due to high cost and technical demands required.

Radiology

It usually takes 2–5 months after onset of the disease to note any radiological changes [30]. The classic triad for TB arthritis is juxta articular osteoporosis, peripheral osseous erosion, and gradual narrowing of intraarticular space. This can be confused for rheumatoid arthritis which has similar findings apart from preserved joint space especially in early TB arthritis [30]. Children may present with enlarged epiphysis. Computerized tomography (CT) and magnetic resonance imaging (MRI) can be used to characterize the disease further. MRI defines soft tissues better, while CT is good for bony lesions. Between the two MRI is the investigation of choice when you want to see the extent and severity of damage. Characteristic findings of TB arthritis on MRI are synovitis, effusion, central and peripheral erosions, active and chronic pannus, abscess, bone chips, and hypointense synovium [31]. These are illustrated in Figs. 18.1, 18.2, 18.3, and 18.4.

Interferon Gamma Release Assays (IGRAs)

These are T-cell assays that measure production of interferon γ in response to stimulation by host blood cells. There are two assays, T-Spot TB and QuantiFERON-TB Gold, that are available. Unfortunately, they can detect active disease and latent tuberculosis infection so interpretation should be done using the clinical scenario [32, 33]. The costs and technical demands of IGRAs have limited their use in resource-poor settings, where better tests are the most needed.

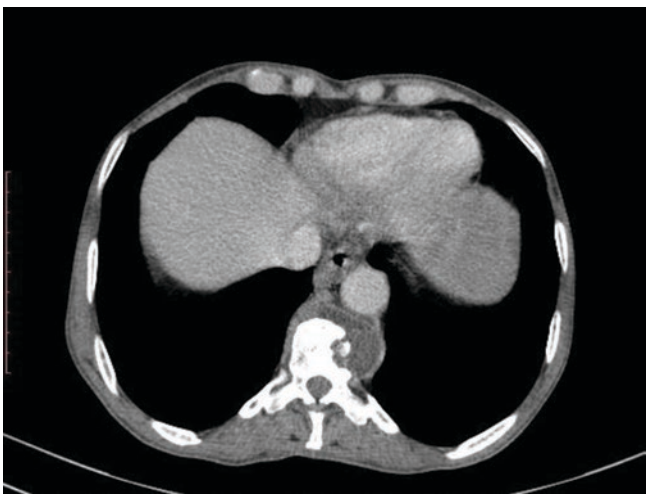

Fig. 18.1 Left paravertebral abscess elevating the aorta in a patient with TB spine adjacent to a Brodie's abscess in T10 vertebra. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

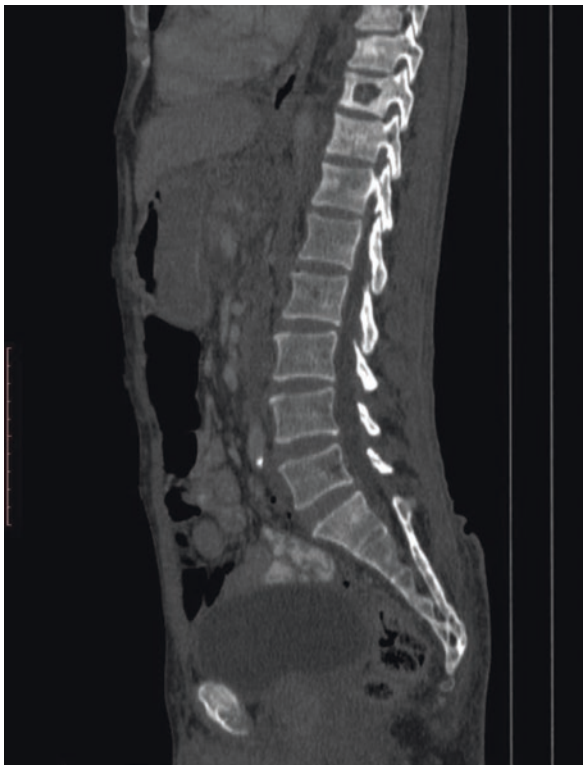

Fig. 18.2 A Brodie's abscess in T10 vertebral body in a patient with TB Spine with paravertebral abscess. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

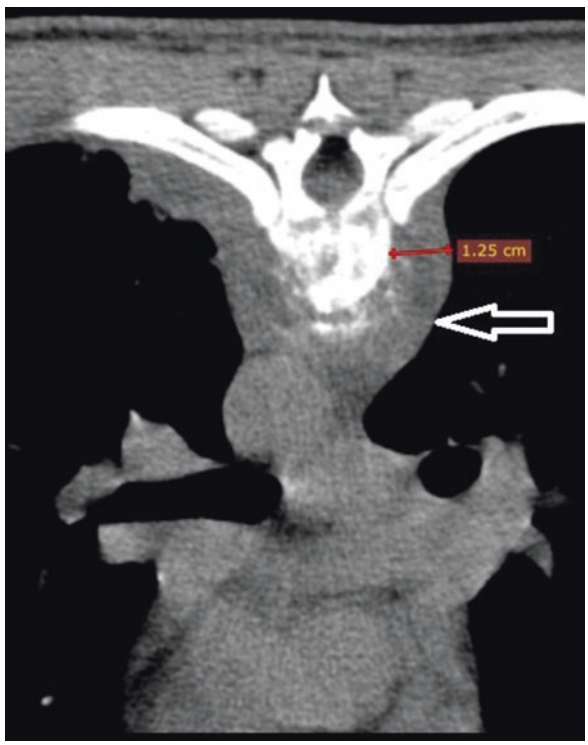

Fig. 18.3 Thoracic spinal TB with paravertebral abscess and vertebral body lysis. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Kenya)

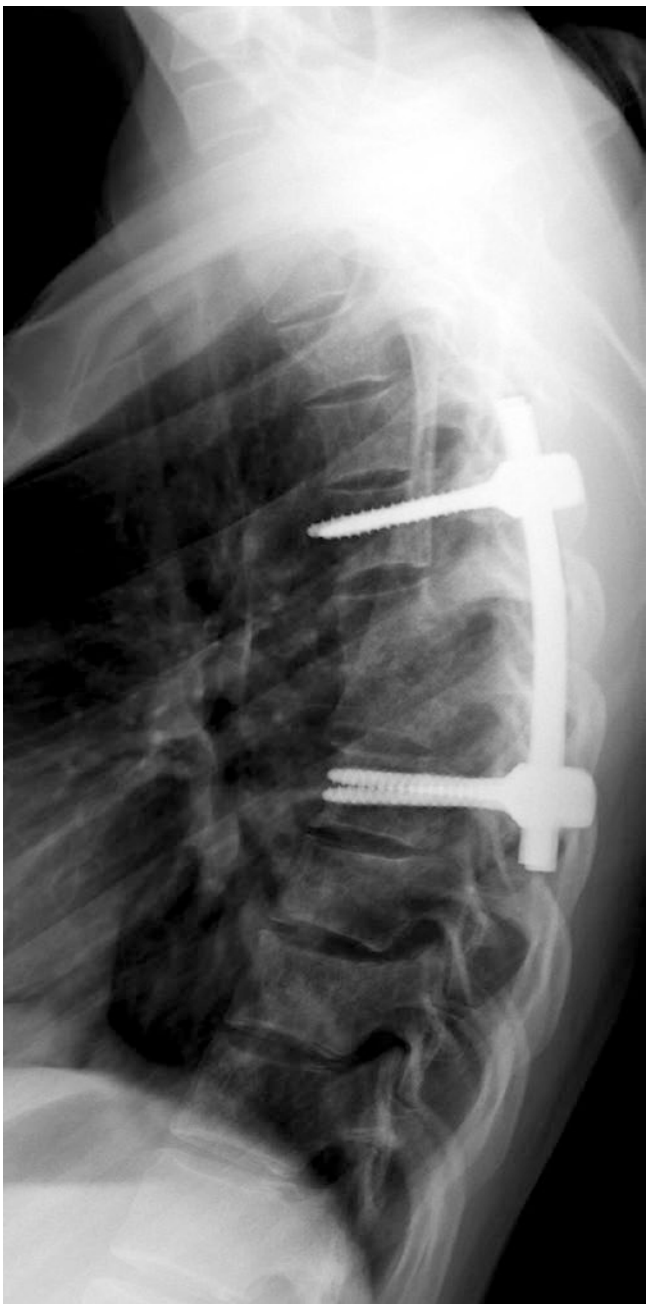

Fig. 18.4 Harrington rod placement to stabilize T5 and T6 vertebrae following collapse fractures secondary to tuberculous spondylodiskitis. (Image courtesy of Dr Elijah Kwasa, Radiologist, Stratus Medical, Nairobi, Kenya)

Tuberculin Skin Test

The Mantoux test is the recommended standard tuberculin skin test [TST]. Tuberculin is commercially available in 1, 2, and 5 Tuberculin Unit (TU) PPD (purified protein derivative, RT23 equivalent) forms. The test is read 48–72 hours after an injection, with raised wheal of about 6 mm identified as positive [34]. In areas of high TB prevalence, the positive predictive value of TST is higher [34]. It is important to note that prior BCG vaccination depending on age at vaccination and time after vaccination when TST was done can influence the results [35].

Differential Diagnosis

Skeletal TB can be confused for subacute or chronic infections due to pathogens or diseases such as *Staphylococcus aureus* osteomyelitis, brucellosis, melioidosis, actinomycosis, candidiasis, and histoplasmosis, depending upon epidemiologic factors. In the setting of Pott's disease, the differentials include degenerative disc and facet joint disease, spondyloarthropathy, vertebral body collapse due to osteopenia (due to a variety of causes such as osteoporosis and chronic corticosteroid therapy), pyogenic spinal infection, and malignancy. The use of imaging will help distinguish these from skeletal TB.

Treatment

The mainstay treatment of tuberculosis arthritis is appropriate anti-TB drug therapy. Early antimicrobial intervention can lead to a near complete resolution and preservation of function. The principles that define treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. However, there is paucity of data on the optimal duration of treatment [36]. For a long time, longer treatment duration was recommended. This was due to concerns about poor drug penetration into osseous and fibrous tissues. However, several studies have shown that 6- to 9-month regimens containing rifampin are at least as effective as longer courses without rifampin [36, 37]. A study from United Kingdom comparing 6 versus 9 months showed a higher rate of relapse (62%) with 6 months; no relapse was observed among patients who received 9 months of treatment [38]. A Chinese study in selected patients combined surgical intervention and shorter duration of therapy of 4.5 months and was as successful as the 9-month course with fewer adverse events reported [39].

Surgical interventions are also used in treatment. They include decompression, use of hardware for stabilization of spine, abscess drainage, and/or debridement of infected material [40, 41].

Indications for surgical intervention include [40, 41]:

- Patients with spinal disease and advanced neurological deficits
- Patients with spinal disease and worsening neurological deficits progressing while on appropriate therapy

- Patients with spinal disease and kyphosis >40 degrees at the time of presentation
- Patients with chest wall cold abscess

Monitoring Clinical Response

This is quite difficult as role of inflammatory markers is limited in skeletal TB. Utilization of clinical symptoms like pain, mobility, constitutional symptoms, and neurological findings is more useful. There is no role to perform serial radiographs since radiographic findings may appear to progress during appropriate treatment [42].

Nontuberculous Mycobacterial Infections

Mycobacteria other than *Mycobacterium tuberculosis* and *Mycobacterium leprae* are generally free-living organisms that are ubiquitous in the environment. There are about 60 of the more than 125 nontuberculous mycobacterial (NTM) species that can cause disease in humans [16]. These can be broadly classified into four clinical syndromes [43]:

1. Progressive pulmonary disease especially in older persons caused primarily by *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*.
2. Superficial lymphadenitis, especially cervical lymphadenitis, in children caused mostly by MAC, *Mycobacterium scrofulaceum*, and, in northern Europe, *Mycobacterium malmoense* and *Mycobacterium haemophilum*; the most common cause in adults, however, is *M. tuberculosis*.
3. Disseminated disease in severely immunocompromised patients.
4. Skin and soft tissue infection usually as a consequence of direct inoculation.

NTM rarely affects skeletal tissue; it more commonly affects soft tissue [16]. Soft tissue infections are due to direct inoculation occurring during penetrating trauma, open surgery (such as mediastinitis and sternal wound infections after cardiothoracic surgery), after injection of steroids or local anesthetics, or following cosmetic surgery, such as abdominoplasty and liposuction [16, 44]. The most commonly isolated mycobacteria are the rapidly growing types, for example, *M. abscessus*, *M. chelonae*, and *M. fortuitum* [44]. The disease an indolent course and presents with painful red to violaceous nodules that can drain serosanguineous material, ulcerate, or spread to deeper tissues and form fistulous tracts. Histology may reveal non caseating granulomas with abundant neutrophils. The acid-fast bacilli test is usually negative [16, 44].

NTM skeletal infections are rare. Risk factors are transplant patients, invasive procedure like in cardiothoracic surgery (sternal osteomyelitis due to *M. fortuitum* or *M. abscessus*) or in isolated cases of *M. xenopi* arthritis after joint arthroplasty [45]. Treatment duration for a minimum of 6 months of specific antimycobacterial chemotherapy is recommended, and the regimen can be extended to 12 or more months in patients with disseminated disease [43]. Surgery is recommended for NTM osteoarticular infections where surgical excision of the infected tissue and/or prosthetic joint removal should be performed [43].

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Leprosy-Associated Arthritis

19

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Introduction

Leprosy is an infectious disease with a gradual presentation caused by the bacteria *Mycobacterium leprae*. Osteoarticular symptoms are part of the clinical presentation and are usually the third most common clinical manifestation after skin and nerve involvement and occasionally can be the initial presentation, leading to some confusion for the right diagnosis. In the presence of arthritis in patients from endemic areas, it is important to have leprosy on the initial diagnostic work up. Conventional treatments control the disease, and anti-TNFs have been used in refractory cases. Paradoxal descriptions of cases in patients receiving anti-TNF therapy have been also described.

Epidemiology

Leprosy is an endemic disease in Brazil with detection rate around 12.2/100 mil inhabitants and is still a public health challenge due to the potential of physical deformities when there is delay in the diagnosis. India, Brazil, and Indonesia account for 80% of the cases diagnosed worldwide [1–3].

Etiology

Mycobacterium leprae is an intracellular parasite with tropism for the skin and peripheral nerves. Around 95% of individuals develop a natural resistance to infection, but susceptibility occurs in 5% due to individual and environmental factors, with a mean period of incubation from 3 to 5 years. The bacterium is an intracellular parasite with an affinity to skin cells and peripheral nerves. Man is considered the only natural habitat of the mycobacterium, and it is usually very difficult to grow in artificial culture media.

Pathogenesis

The pathogenesis of the articular disease is still not fully known, and it is believed to be due to either the presence of the bacteria in the joint or an immune reaction to the release of the antigens of the mycobacteria on the so-called reversal reaction (RR).The reactive episodes are known as Type 1 or reversal reaction, and Type 2 erythema nodosum leprosum (ENL) due to direct invasion of the mycobacteria and peripheral neuropathy (Charcot's disease).

The RR inflammatory cytokines induce the Th1 reaction (IFN-gamma, TNF-alpha, and IL-2) and follow injury to the joint and nerves. TNF overexpression is found in the joints and nerves during the episodes and is considered a major cytokine on the process. In ENL one can find, besides TNF, neutrophil cellular infiltration and complement activation associated with the inflammatory reaction and increased expression of cytokines of the Th2 profile (Il-4, IL-10) [4]. In neuropathy the lesion is filled with macrophages of bacilli similar to what is observed on the skin, and the injury appears to be mediated by cytotoxic CD4 T lymphocytes, causing the loss of myelin on the nerve sheath.

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_19

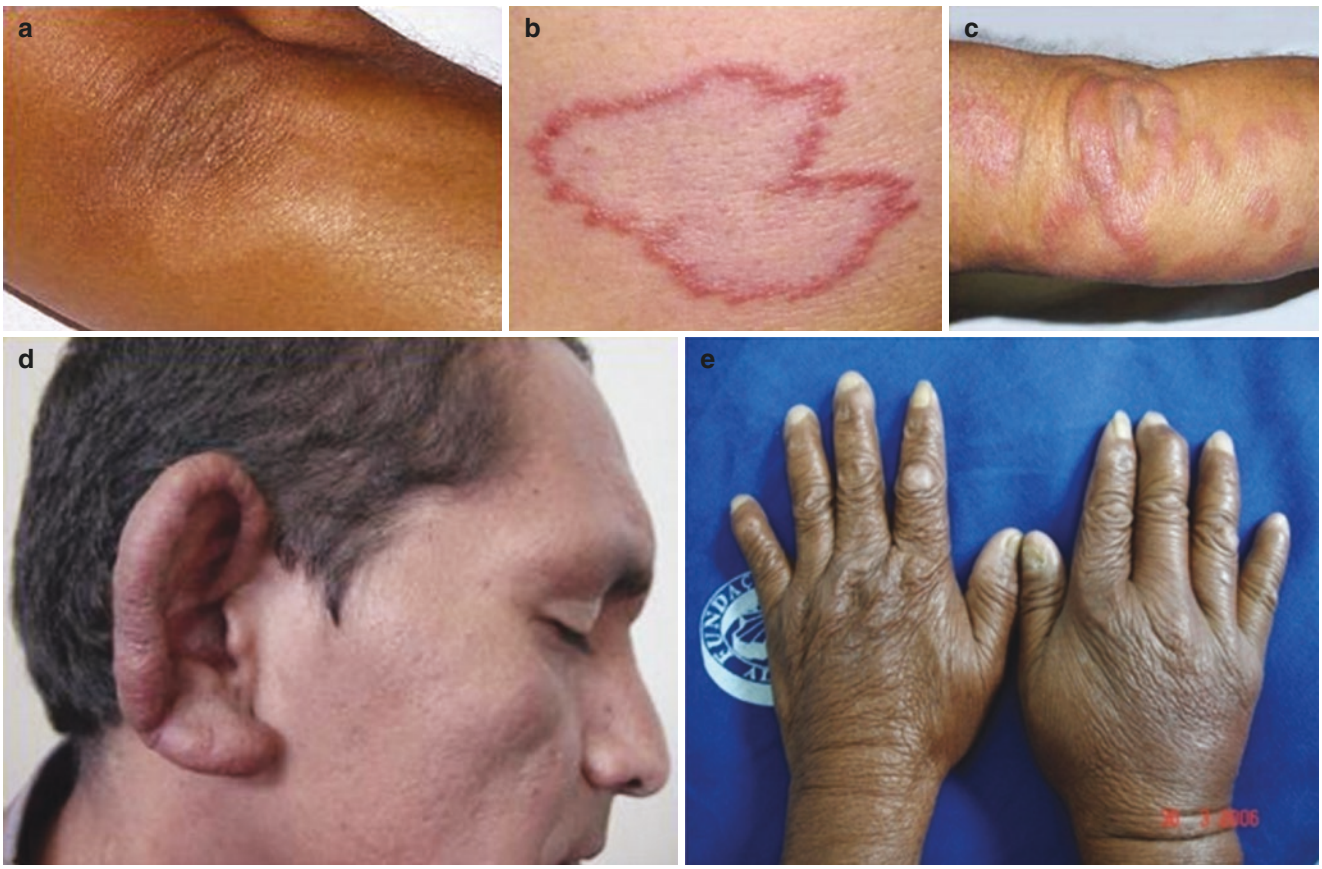

Fig. 19.1 Clinical expression of leprosy. (**a**) Indeterminate, (**b**) Tuberculoid, (**c**) Borderline, (**d**) Lepromatous, (**e**) Reactive inflammatory hand, neuropathy and arthritis

A recent finer study was reported showing evidence that the subtype memory T cells are involved in the development of ENL. Results showed the median percentage of activated T-cells (effector memory and effector T-cells) was significantly increased in patients with ENL (59.2%) before treatment compared to after treatment with prednisolone (33.9%) ($P < 0.005$). This is the first work which has shown T-cell activation and the different subsets of memory T cells in untreated patients with ENL. Consequently, this study delineates the role of T-cell activation in the pathogenesis of ENL reaction and challenges the long-standing dogma of immune complex as a sole etiology of ENL reaction. However, the same group has also shown B cell activation and increased expression of B memory cells in the same group of patients suggesting that both T and B cell memory subtypes actively participate on the cellular pathogenesis of ENL [5, 6].

Clinical Aspects

General Considerations

It is well established that the disease is characterized by two different clinical and immunopathologic stable polar points, the tuberculoid form (TL) where the immune reaction is vigorous and the lepromatous (LL), also known as Virchowian, where the absence of an efficient immune reaction is associated with bacilli multiplication and disease dissemination. Intermediate forms can be found with gradual response against the bacilli that can migrate to the polar states [7]. In a recent 5-year review (2010–2015) in Brazil of clinical presentations, the authors in the city of Campinas showed the frequency of clinical forms of leprosy in patients that presented with leprosy reactions. The majority of patients had the Virchowian form, confirming reports from longer periods from other countries [8, 9] (Figs. 19.1 and 19.2).

Articular Manifestations

Articular manifestations occur in around 3% of the leprosy population when large series are reported with a higher frequency on hospitalized patients. The presence of arthritis is frequent in the reactional states but can also occur in isolated form throughout the disease period. Specific types described are:

1. Neuropathic form of arthritis
2. Septic arthritis where one can find the bacteria on the joint
3. Osteoarthritis associated with pyogenic dissemination having originated with the presence of skin ulcers

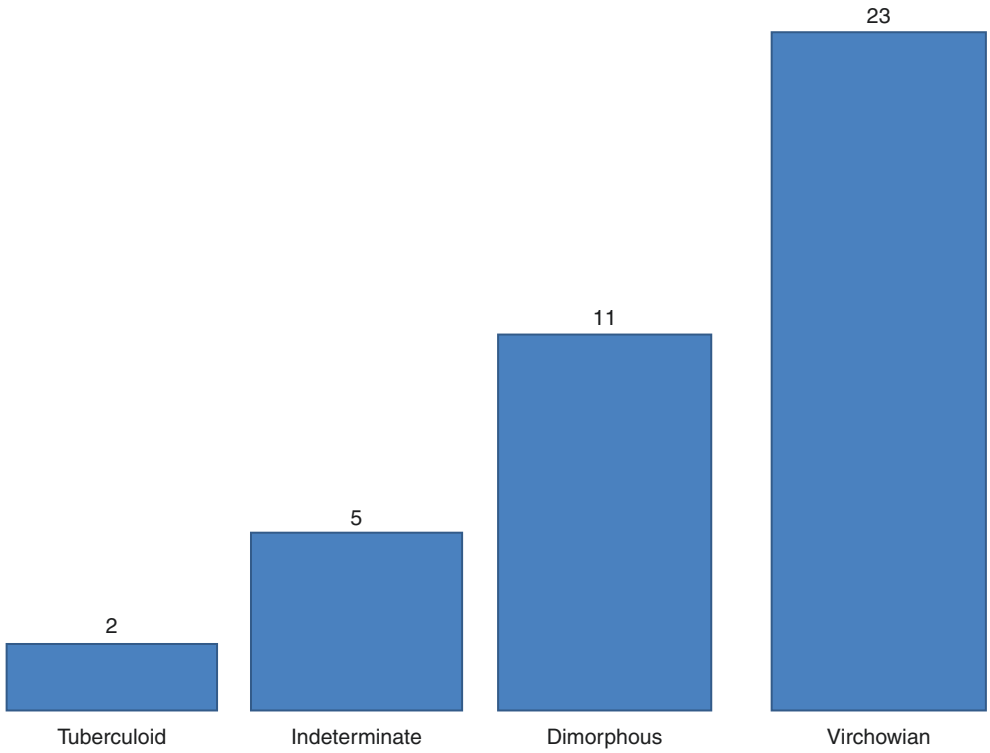

Fig. 19.2 Clinical forms of leprosy in patients that presented leprosy reactions

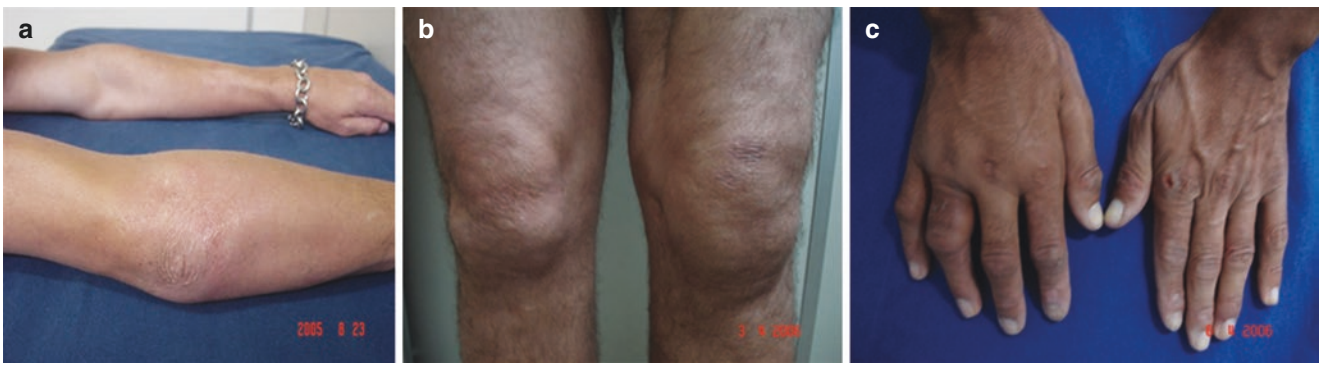

Fig. 19.3 Manifestations of leprosy arthritis. (**a**) Tuberculoid leprosy reactive oligoarthritis, (**b**) Reverse reaction, (**c**) Joint inflammation mimicking rheumatoid arthritis

A not well-defined form of arthritis is also described independent of the simultaneous presence of active bacillary disease.

Articular Manifestations in the Reactive States

Articular manifestations are commonly seen in the Type 1 or RR with polyarthritis, with initial acute or subacute occurrences predominantly on the hands and wrists, more often seen close to skin lesions. The clinical presentation can precede or be associated with other clinical manifestations. In Type 2 or ENL, the clinical picture is more of a generalized polyarthritis transient in nature, usually 1 or 2 weeks, and associated with skin lesions presenting with vesicle-bullous and pustulous ulcers. Constitutional symptoms like fatigue, Raynaud's, neuritis, nephritis myositis, and adenomegaly are usually seen. The duration of the symptoms depends on the response to treatment but usually disappears after 1 or 2 weeks without sequelae (Fig. 19.3).

Arthritis Non-related to Reversal Reactions

Charcot Arthritis, also known as neuropathic, presents with subluxation of joints, fracture, and deformities in large joints. It is seen in all forms of the disease but is more common in the lepromatous form, contrary to the arthritis related to

reversal states, and is often persistently resistant to the use of non-steroidal anti-inflammatory drugs and antimicrobial agents [10–15].

Osteoarticular Manifestations in Leprosy
- Chronic symmetrical polyarthritis
- Tenosynovitis
- Destructive Osteitis
- Neurogenic bone destruction (Charcot)

As briefly mentioned previously, the study in Campinas Brazil showed that the majority of patients with leprosy reactions had the Virchowian form [8].

Laboratory Tests

The majority of the laboratory changes are of a non-specific nature. Acute phase reactants are elevated including C reactive protein and sedimentation rate. Several autoantibodies can be found including antinuclear antibodies, rheumatoid factor, anti-citrulline (CCP2 -CCP3), anti-DNA, anti-neutrophil cytoplasm antibodies (ANCA), anticardiolipin, and anti-Beta 2 glycoprotein antibodies. These autoantibodies are more commonly seen in the lepromatous form, and their presence is variable. With TT, the cellular response is efficient, and the presence of autoantibodies is significantly small. The evaluation of isolated articular manifestations and positivity for autoantibodies can lead to the erroneous diagnoses of rheumatoid arthritis and lupus erythematosus. Our group has evaluated this particular topic of the possible presence of anti-phospholipid antibodies and the diagnosis of rheumatoid arthritis, by looking at specific antibodies such as anticardiolipin and anti-citrulline. We found low incidence of anticardiolipin and anti-CCP3 antibodies and no thrombosis. In one of those studies from our own group we assessed the prevalence of autoantibodies in patients with leprosy. Forty-one cases of lepromatous leprosy were studied. For the detection of autoantibodies we used the Elisa technique using the following purified antigens: dsDNA, ssDNA, histone, mitochondria, RNA, RNP, SS-A, SS-B, Sm, Scl-70, Anca C, Anca P, and the cardiolipin complex. As a "cut off" point we used values shown on previous studies to differentiate normal from elevated values. Antibodies to SS-B, mitochondria, and cardiolipin were the most prevalent in our study.

Anti-mitochondrial antibodies distinct from those seen in primary biliary cirrhosis and antiphospholipid antibodies with variable ligand activity to B2GIP are frequent in the sera of leprosy patients. In another study we analyzed in detail the presence of anti-mitochondrial antibodies in leprosy patients. In sera from 69 patients with leprosy but without liver involvement we assayed for the presence of mitochondrial pyruvate dehydrogenase (PDH)-specific autoantibodies by enzyme-linked immunoabsorbent assay (ELISA), immunoblotting using PDH as an antigen, and enzymatic inhibition test. Twenty-seven of the leprosy serum samples (39.1%) were found to react with PDH by ELISA. However, unlike sera from primary biliary cirrhosis (PBC) patients, none of these were able to inhibit the PDH enzymatic activity. By immunoblotting, it was found that only two of the 27 positive sera recognized the 74-kD protein of the PDH complex, which is recognized by sera of most PBC patients. The anti-mitochondrial antibodies in lepra most probably recognize different epitopes than those in PBC. These findings may indicate that anti-PDH autoantibodies in patients with leprosy may arise by polyclonal B cell stimulation and may represent natural anti-PDH autoantibodies. Finally the complement system was reviewed in a very recent paper; it was possible to show that Complement C1q is implicated in the pathogenesis of ENL. The authors showed a decreased circulating C1q suggesting the utilization of C1q in immune complex formation in these patients. They also suggest the possibility of becoming a potential diagnostic marker for active ENL reactions. The routine serology that should be performed to confirm leprosy arthritis and exclude autoimmune disease and leprosy:

Laboratory Diagnoses of Leprosy and Arthritis
- Antinuclear antibodies
- Anti-DNA antibodies
- Anticardiolipin antibodies
- Anti-beta2-glycoprotein antibodies
- Anti-cyclic citrullinated peptide antibodies
- Anti-mitochondrial antibodies
- HLA typing (B27 human leucocyte antigen)
- Synovial fluid analysis

In a more recent study from the southern part of Brazil the authors looked on the concomitancy of positivity for rheumatoid factor and anti-CCP in leprosy proved diagnosis. A high frequency of RF positivity was observed among the leprosy patients (41.2%, 40/97), with RF immunoglobulin A (IgA) significantly associated with arthritis (OR = 7.9, 95% CI = 1.5–40.6 $P = 0.008$). Anti-CCP was observed in 9.3% (9/97) of the patients, with anti-CCP2 being the most frequent subtype. Only 4.1% (4/97) of the patients were RF and anti-CCP concomitantly positive. RF IgM showed a significant association with leprosy when compared to healthy controls ($P < 0.0001$), whereas for anti-CCP2 no significant results were observed ($P = 0.0585$).

The synovial fluid shows variable cellularity with predominance of neutrophils or non-inflammatory with mononuclear cells and presence of bacilli. On the synovial biopsy synovitis with neutrophil infiltration and sometimes with identification of bacilli can be found [16–25].

Radiology in Leprosy

Osteoarticular radiological findings are specific and non-specific and secondary to the joint inflammatory activity and osteoporosis. Soft tissue swelling, bone resorption, multiple cysts bone necrosis, osteitis, and signs of osteomyelitis can be found. Periosteotitis is seen in the interphalangeal proximal and distal and also in long bones and signs of destructive arthritis.

On the non-specific changes one can find hypertrophic sclerotic changes, osteophytes, and also atrophic changes with bone resorption and a picture known as "licked candy stick." Specific changes found include osteopenia, erosions narrowing of the articular space, and seldom sacroiliitis. Modern image techniques have been applied to the management of leprosy patients; ultrasound, magnetic resonance, and PET-CT were able to detect nerve thickening in such patients [26–28].

Diagnosis

The diagnosis of leprosy can be difficult especially when the patient is not in endemic areas and the prevalence is low. Similarities between tenosynovitis arthritis and rheumatic autoimmune diseases can be striking; however, the combination of arthritis tenosynovitis and paresthesia raises a strong suspicion that infection with Mycobacterium leprae is present. It is well known that arthritis is common in reactive states. In a 20-year retrospective evaluation in Thailand the authors showed leprosy reactions are common complications in leprosy patients. Being female, positive bacillary index status, and multibacillary treatment regimen are significantly associated with the reactions. Early detection in cases with risk factors followed by appropriate treatment could prevent the morbidity of leprosy patients [9].

Treatment

Non-steroidal anti-inflammatory drugs corticoids in low doses (thalidomide and methotrexate) are the medications used in arthritis associated with leprosy. The presence of neuritis reactive hand disease and eye involvement requires higher doses of steroids. Although less used, sulfa derivatives and cloroquine have been also employed. Favorable responses are seen in a 2-week period. There are a few cases reported showing the beneficial response with anti-TNF agents in refractory cases; however, there are reports of possible anti-TNF-inducing leprosy, similar to what is shown in psoriasis, for instance, of a 37-year-old woman with RA receiving an anti-TNF agent who developed a rash on her back and both legs, which was finally diagnosed as tuberculoid leprosy [29–33].

Prognosis

The earliest diagnosis and the adequate treatment for the disease in the reactive stage are important strategies for the prevention of physical deformities and irreversible movement limitations, except in the presence of pathological fractures.

Conclusions

Leprosy-associated arthritis is a treatable disease, but diagnosis can be overlooked if one does not consider the differential diagnosis of muscle skeletal symptoms, especially if the patient lives or comes from an endemic area. The development of leprosy depends on genetic background and the immune status of the host. However, there is no systematic view focusing on the biological pathways, interaction networks, and overall expression pattern of leprosy-related immune and genetic factors. A list of 123 differentially expressed leprosy-related genes, which were enriched in activation and regulation of immune response, was obtained in a reported analysis. Cross-disorder showed that the list of leprosy susceptibility genes was largely shared by typical autoimmune diseases such as lupus erythematosus and arthritis, suggesting that similar pathways might be affected in leprosy and autoimmune diseases. Our analyses showed that leprosy-associated genes constituted a co-evolution network and might undergo positive selection driven by M. leprae. We suggested that leprosy may be a kind of autoimmune disease, and the development of leprosy is a matter of defect or over-activation of body immunity [33].

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Coccidioidal Arthritis

20

Andrés Felipe Echeverri

Introduction

Coccidioidomycosis is an invasive fungal infection caused in humans by the dimorphic fungus of the *Coccidioides* genus. Two species are known: *Coccidioides immitis* and *Coccidioides posadasii*, which differ genomically but are indistinguishable from a morphological and clinical standpoint [1] (Table 20.1). The fungus is distributed in dry and hot areas with low levels of rainfall, such as the southwestern United States and some areas of Mexico and South America [2].

Its infection is spread by the aspiration of airborne spores known as arthroconidia, produced in the saprophytic phase of the fungus. Once in the lungs, these spores can be asymptomatic or cause cough, dyspnea, fever, fatigue, and arthralgia; this syndromic picture is popularly known as Valley Fever or Desert Rheumatism.

It is known that certain conditions such as immunodeficiency, pregnancy, diabetes mellitus, HIV infection, and certain ethnic groups have a higher risk of disseminated infection. Dissemination via hematogenous or lymphatic spread may cause involvement of any organ or system; however, the skin, bone, lymph nodes, and central nervous system (CNS) are the most common [2].

Skeletal manifestations occur in approximately 25% of the individuals with disseminated coccidioidomycosis, which may affect both the axial and appendicular skeleton. Early diagnosis and adequate antifungal therapy are essential to avoid bone damage and irreversible functional sequelae [3].

Definition

Coccidioidomycosis is a disease caused by a dimorphic fungus of the genus Coccidioides; it can affect both humans and animals. It is also known as San Joaquin Fever or Valley Fever, and is characterized by fever, cough, arthralgia, and fatigue. Five percent of patients may develop disseminated forms of the disease, especially those in conditions of vulnerability [4]. Osteoarticular involvement occurs in up to 25% of subjects with disseminated disease. Osteomyelitis is the most frequent manifestation, although patients may also develop arthritis, tendonitis, or muscle abscesses [3].

Epidemiology

Most cases of coccidioidomycosis are found in hot and dry regions characterized by low rainfall and alkaline soils, such as the southwestern United States [2, 5]. The areas with the highest prevalence of the disease are the states of Arizona,

Table 20.1 Differences between *Coccidioides* species

Coccidioides species	Genes	Endemic areas	Culture	Serologic testing	Clinical manifestations
immitis	10,355	Desert regions of Central and Southern California (including Lower California)	Sabouraud-dextrose, blood, and chocolate agar 1–3 weeks	No differences	No differences
posadasii	7229	Nevada, Arizona, New Mexico, Western Texas, Mexico, Central, and South America	Sabouraud-dextrose, blood, and chocolate agar. 1 week Faster than *immitis* at higher temperatures	No differences	No differences

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_20

California, Nevada, Utah, New Mexico, Washington, and Texas. Even some areas within Arizona (Phoenix and Tucson) and California (Bakersfield) are considered highly endemic [5, 6]. In Arizona, two peaks of high activity of the disease have been described in the spring and at the end of the summer, and in California one at the end of the summer [4]. The annual incidence of coccidioidomycosis in these areas is quite variable, although over time a significant increase has been noted. According to reports from the Centers for Disease Control and Prevention (CDC) in 2011, the incidence was 42.6 cases per 100,000 inhabitants and was higher among people aged between 60 and 79 years [7].

Globally, areas in Mexico, Guatemala, Honduras, Venezuela, Brazil, Paraguay, and Argentina that meet the appropriate climatic features bear endemic regions for the disease [8, 9]. In Argentina historically, Posadas A. was the one that reported the first case of coccidioidomycosis in 1892, and this was the starting point of a description and a more detailed knowledge of the disease [10].

In endemic areas, certain occupations as construction workers, archeologists, and farmers are at high risk of acquiring the infection [11]. The most common clinical manifestation is pulmonary; in areas of high prevalence, it is estimated that approximately 30% of community-acquired pneumonia is due to coccidioidomycosis [5, 12]. In the disseminated forms of the disease, there may be involvement of any organ or system, and it is estimated that less than 5% of immunocompetent individuals present with it [13, 14].

Population studies associate blood groups A and B, along with HLA class II DRB1∗1301 alleles as risk factors for severe and disseminated forms [15]. Similarly, African Americans and Filipinos have a higher risk of dissemination compared to other ethnicities, although in the primary forms of the disease, racial difference is not as marked [6, 13]. Approximately 5% of patients may present disseminated forms of the disease, especially those with more susceptible conditions [4]. Risk groups for disseminated forms include subjects with HIV-infection, transplantation, diabetes, autoimmune diseases, use of immunosuppressants, and pregnant women [16–19]. Skeletal involvement can occur in up to 25% of the patients with disseminated coccidioidomycosis.

Etiopathogenesis

The microorganism has two phases in its life cycle: saprophytic and parasitic. In the saprophytic phase, it exists in the soils of arid zones. The endospores grow and mature, forming septate hyphae and mycelia. These mycelia are fragile and easily fractured with heat and wind; the remaining fragments are simple spores called arthroconidia. These structures that are potentially infectious have the ability to unravel from the mycelia and become airborne. At this point, arthroconidia can return to the floor or be inhaled by the host. In case of being inhaled, they begin their parasitic phase in the lung. First, they acquire a spherical form and start to grow through wall thickening and an internal multinucleation process; this structure is called spherule. The spherules begin to divide internally through invagination, producing multiple uninucleated endospores. When the spherules break, the endospores can reach the ground again and start a new cycle in its saprophytic phase or continue with the formation of more spherules in the lung [4, 7].

Once the infection occurs there is a response of the innate immune system, with the activation of the complement system and the release of chemotactic factors in the tissue. Subsequently, the macrophages and neutrophils try to eliminate the infection, but it has been described that the endospores, the arthroconidia, and especially the spherules, are quite resistant to phagocytosis and destruction. It has been proposed that the spherules produce a large fibrillary matrix and extracellular oxidoreductases that do not allow a proper approach of the immune system cells which protects them from the attack by neutrophils [8, 20]. Cellular immunity is activated, and increased concentrations of tumor necrosis factor alpha, interleukin 17, and interferon gamma have been evidenced in subjects with pulmonary coccidioidomycosis [21]. The immune response of the host, the size of the inoculum, along with the specific characteristics of resistance and virulence of the Coccidioides, are important to determine the severity of the disease; most of the infections are self- limited, and these patients generate a delayed hypersensitivity that can be determined by the positivity of spherulin and coccidioidin cutaneous tests. Conversely, in patients with disseminated coccidioidomycosis, high titers of complement fixation antibodies and absence of late hypersensitivity are found [14].

Lymphatic and hematogenous dissemination can occur to any organ or system, the skin, subcutaneous tissue, skeletal system, meninges, and lymph nodes being the most prevalent. The infestation by direct inoculation of arthroconidia in the subcutaneous tissue can occur, but it is uncommon [4].

Clinical Manifestations

Coccidioidomycosis has a fairly wide spectrum and presentation; in endemic areas, 60% of the subjects with positive cutaneous tests (spherulin or coccidioidin) never experienced symptoms or suffered self-limited forms of the infection. The other percentage may have mild forms of the disease to severe clinical conditions, which can even lead to patient death [6].

The initial symptoms are quite nonspecific (fever, fatigue, arthralgia, myalgia, and malaise); thus, the suspicion must be given in relation to the exposure in risk sites and the prevalence of coccidioidomycosis in the area. The lungs being the site of fungal entry into humans, symptoms such

as cough, dyspnea, and chest pain are frequent. This clinical picture starts from 1 to 3 weeks after the inhalation of arthroconidia. During this phase, some patients may experience significant functional impairment; hence, the popular name of "desert rheumatism."

From the dermatological point of view, at the beginning of the disease between 10% and 50% of individuals can present transitory cutaneous manifestations which are secondary to the immunological phenomenon triggered by the infection; the most frequent are erythema nodosum and erythema multiforme [4]. Dissemination occurs in less than 5% of immunocompetent patients. In the next section, some of the clinical manifestations by systems will be discussed, with special emphasis on musculoskeletal involvement.

Pulmonary Involvement

Pulmonary involvement is the most frequent clinical manifestation. It is estimated that, in areas of high endemicity, the disease is responsible for approximately 30% of the cases of community-acquired pneumonia [12]. The spectrum of severity of the symptoms is quite variable. In most patients the course is asymptomatic or may present with fever, cough, dyspnea, and fatigue that can be self-limiting in a few days. Sometimes, symptoms may persist or worsen and progress to lobar or segmental pneumonia. Many of these patients receive antibiotic management for bacterial pneumonia before the diagnosis of coccidioidomycosis is established.

Diffuse pneumonia is one of the most serious complications related to coccidioidomycosis. Radiographic findings show diffuse multilobar infiltrates and hilar adenopathies. The immunocompromised state of the patient, along with a large inoculum size, has been considered risk factors. The delay in the diagnosis and initiation of therapy can trigger an adult respiratory distress syndrome, which can threaten the patient's life [5].

Pleural effusion may be present in up to 15% of patients with pneumonia, and a quarter of these can be complicated by empyema [22]. Approximately 5% of the patients, after the resolution of the acute pulmonary infectious process, develop lung nodules or small cavitations as sequelae, which in most cases are incidental findings in the radiological studies, especially in subjects where no previous diagnosis of coccidioidomycosis was established. Frequently, these nodules or cavitations are asymptomatic and require only routine clinical and radiological follow-up. Other patients may present chest discomfort and hemoptysis; in these cases, the use of antifungal therapy may be indicated. These cavitations rarely present ruptures, causing pneumothorax or bronchopleural fistulae [4, 5, 13].

Disseminated Coccidioidomycosis

Disseminated coccidioidomycosis may involve any organ or system, and is acquired by hematogenous or lymphatic spread from the lung. Patients with HIV-infection, immunosuppression, diabetes, pregnancy, and certain ethnic groups such as African Americans and Filipinos have a greater risk of dissemination [5, 6]. Dissemination mainly occurs to the skin, subcutaneous tissue, lymph nodes, skeletal system, and meninges, although there are descriptions of unusual manifestations such as prostatitis, pericarditis, peritonitis, and parapharyngeal abscesses, among others [23].

Musculoskeletal Involvement

Skeletal affection can occur in 20–25% of the individuals with disseminated coccidioidomycosis; it can affect any bone or adjacent structures. It is a chronic and destructive condition which can lead to severe functional impairment. Osteomyelitis is the most common clinical manifestation; it mainly involves the axial skeleton but also affects the appendicular component. At the axial level, the most affected structures are vertebrae (mainly thoracic). The involvement at this level can be either single or multiple and can cause fractures. Initially, it can be misdiagnosed with other granulomatous diseases like tuberculosis or mimic metastatic lesions or malignancy [24]. Skull, sternum, and rib involvement is unusual but has also been described [25]. At the peripheral level, the malleoli of the ankles, the tibial tuberosity, and the radial styloid of the wrists are common sites affected, although any bone can be compromised [24].

Joint involvement may or may not be accompanied by osteomyelitis, although being less frequent. The most affected joints are those of the lower limbs, with the knees being the most compromised. It is usually monoarticular, with synovitis and joint effusion [3]. The synovial fluid can demonstrate an exudate, and the cultures can be positive in about 50% of the cases [26]. Histopathology of the synovial tissue exhibits granulomatous inflammation and spherules [24]. Long bone X-rays may show single or multiple lytic lesions with irregular edges and osteopenia [3]. Bone scintigraphy is useful to search for osteomyelitis foci; tomography helps to determine the level of bone destruction, and magnetic resonance imaging with gadolinium is important to assess the extension of the disease, mainly to soft tissues and adjacent structures [25]. Tenosynovitis and psoas muscle abscesses are uncommon manifestations that occur mainly by continuity of the infectious process in patients with osteomyelitis [27–29].

Coccidioidal Meningitis

Coccidioidal meningitis is the most severe and lethal extrapulmonary manifestation of coccidioidomycosis. Headache is the most common symptom; it is associated with blurred vision, photophobia, meningismus, and changes in mental status. The most frequent complication is hydrocephalus, although vasculitic infarcts, thrombosis, and arachnoiditis may also occur.

The diagnosis is established with the study of cerebrospinal fluid, serological tests, and cultures. Timely and effective treatment is essential to avoid sequelae and improve the survival of patients [5]. Fluconazole is the drug of choice for the management of meningeal coccidioidomycosis [30]. As alternatives, the other azoles and amphotericin B can also be used. Indefinite treatment is recommended since there are reports of relapse with its withdrawal [31].

Cutaneous Coccidioidomycosis

Cutaneous coccidioidomycosis can present as an immunological reaction secondary to pulmonary infestation such as erythema nodosum, erythema multiforme, or acute exanthema, which are usually transient and, in most cases, do not require any specific treatment other than disease control.

Skin involvement secondary to disseminated infection has been described between 15% and 67% of the individuals [32]. The heterogeneity of the lesions is quite variable; the presence of nodules is the most predominant, although papules, warty plaques, ulcers, abscesses, and fistulae have been described. The sites of greatest commitment are face, neck, scalp, and chest [33]. Fluconazole and itraconazole are the first line drugs recommended for treatment, although the new azoles (posaconazole and voriconazole) and amphotericin B may be used as alternatives in refractory cases [34].

Diagnosis

The diagnosis is initially difficult, even in areas of high endemicity, due to the non-specificity of acute symptoms. The occupation of the patient, the trips to desertic areas among others, should increase our suspicion of the possibility of coccidioidomycosis. It is noteworthy that an early diagnosis is necessary to prevent chronic infections and associated functional sequelae.

Conventional laboratories may show an elevation of erythrocyte sedimentation rate, leukocytosis, and eosinophilia. Eosinophilia, particularly, can help differentiate a community-acquired pneumonia of bacterial origin from coccidioidal pneumonia, taking into account other differential diagnoses that can generate confusion, such as eosinophilic pneumonia [13].

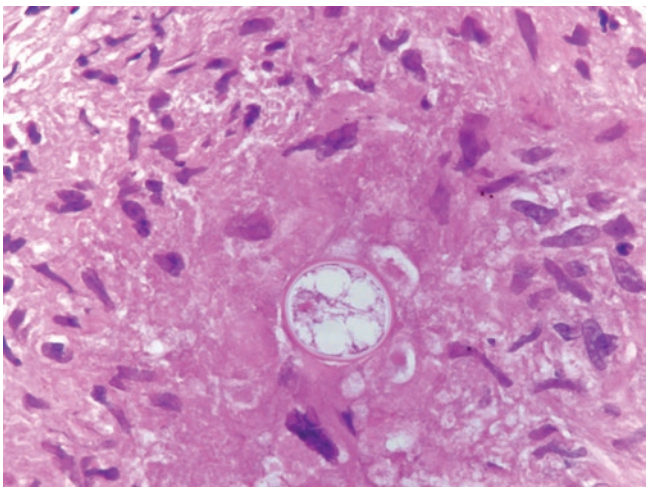

Fig. 20.1 Spherule visualization in a tissue sample of a patient with disseminated coccidioidomycosis. Hematoxylin eosin stain. (Courtesy of Alejandro Velez MD. Pathology Department, Hospital Pablo Tobón Uribe. Medellin-Colombia)

Definitive diagnosis must be established with culture or isolation of the fungus in examined biopsies or tissues, although the isolation in sputum, synovial, and cerebrospinal fluids can also establish the diagnosis (Fig. 20.1).

In tissues, spherules or endospores, characteristics of the parasitic phase of the fungus can be visualized; micellar forms are rarely observed, but there are reported cases of patients with chronic infection and diabetes mellitus in which they have been isolated [35]. Furthermore, a granulomatous reaction with fibrosis and caseous can be found in more chronic lesions [6].

The serological assessment to be initially performed in patients with suspected coccidioidomycosis includes IgG and IgM antibodies by enzyme-linked immunoassays (EIA). Positivity of these tests is highly sensitive for coccidioidomycosis infection, but with low specificity. Moreover, the negativity of results does not rule the infection. The timing for this measurement should be considered since the antibodies become positive weeks to months after the beginning of the disease; thus, in the early stages they may be undetectable, especially if the patient is immunocompromised [36]. In these cases, if there is a high suspicion of coccidioidomycosis, these tests must be repeated a few weeks later, considering the seroconversion.

Due to the low specificity of the EIA tests, it is recommended to confirm with the immunodiffusion tests, which are more specific. It is reported qualitatively with IgG or IgM antibodies. Once confirmed, it is recommended to perform the complement-fixation test, which provides additional quantitative information as titers. It has been considered that

titers greater than 1:16 are suggestive of dissemination [13]. Tests for measuring coccidioidal antigen in serum and urine are not for routine use; its utility has been described in severely immunosuppressed subjects with disseminated disease in which the serological tests are negative [37]. PCR-based tests for coccidioidomycosis have shown satisfactory results in lung samples but very poor performance in other types of fluids, with an important negative predictive value [38].

Spherulin and coccidioidin cutaneous tests are useful for epidemiological studies, such as those that wish to evaluate prevalence. A positive reaction is considered evidence of exposure or a previous infection. They are used in subjects who have developed pulmonary infection to assess delayed cell-mediated immune response [39]. These cutaneous tests must not be used as diagnostic tests.

Treatment

Before defining the type and duration of treatment, the involved system, severity, and extension of the disease must be considered, taking into account the possibility of tissue affection, including muscle, tendons, subcutaneous tissue, and skin. The presence of primary lung involvement, severe or progressive disease, together with high-risk dissemination groups makes treatment mandatory. The 2016 IDSA guidelines recommend that those subjects with non-complicated pneumonia without debilitating symptoms, as well as those with asymptomatic pulmonary nodules, should not receive antifungal therapy [30]. In disseminated forms, all patients should receive management; azoles such as fluconazole and itraconazole are the most commonly used. Amphotericin B is reserved for the most severe cases and for those individuals who have failed to therapy with azoles [13]. In patients with bone or joint involvement, it is recommended to start with fluconazole 800 mg per day or itraconazole 200 mg twice a day. There is a double-blind randomized study comparing the effectiveness in managing extrapulmonary affection between itraconazole and fluconazole; itraconazole showed to be more effective than fluconazole in the treatment of osteoarticular involvement [40].

Amphotericin B is used in severe bone or joint affection at a dose of 5 mg/kg IV per day in lipid complex presentation, and liposomal 3–5 mg/kg IV per day until stabilization or improvement of the infectious process, and then it is switched to azoles. There is no definite time for therapy; it should be guided by the clinical response, the complement-fixation titles, and the normality of other laboratory parameters that might be altered [3]. Surgical management must be considered in large abscesses, sequestrum, and spinal instability due to vertebral fractures. In the latter, it is important to have the support of a neurosurgeon who can determine a surgical emergency [3].

New azoles such as posaconazole and voriconazole have shown in vitro effectiveness against Coccidioides and have been used as alternative therapies when fluconazole and itraconazole fail [41]. In some case reports of refractory patients, echinocandins, such as caspofungin, are used in combination with azoles and amphotericin B with good effectiveness, but not as monotherapy [5, 42].

Interferon-gamma is used as a saving adjuvant therapy in critically ill patients, considering the importance of cellular immunity in the control of coccidioidomycosis. However, the cost of therapy, side effects, and lack of clinical studies in disseminated coccidioidomycosis are its limitations [6, 43].

Prognosis

Coccidioidomycosis in general has a good prognosis given the asymptomatic course in 60% of patients. In disseminated forms, the favorable prognosis depends on a timely diagnosis and the rapid establishment of antifungal therapy. It is known that untreated meningeal coccidioidomycosis is lethal in all subjects [44]. At the bone level, fractures may be present in the compromised bones. In the vertebrae, there may be instability with a risk of spinal cord compression with the requirement of urgent surgical treatment. The duration of antifungal therapy is not clearly defined, but it must be for a long time and until there is evidence of improvement of clinical and laboratory parameters of the patient. A routine clinical follow-up to evaluate possible relapses must be conducted [3].

Future Directions and Conclusions

Nikkomycin Z is a derivative of the polyoxins that acts by inhibiting the synthesis of chitin. It has demonstrated antifungal activity against Coccidioides in vitro and in animal models. It is in experimental phase and is one of the most promising therapies for the management of mycosis caused by dimorphic fungi [45].

Vaccination is an interesting option that can prevent serious manifestations or reduce the incidence of infection in susceptible populations. Greater knowledge on the fungus genome and the possibility of using its protein compounds have allowed advancing in the study of possible recombinant vaccines, currently being tested in animal models with satisfactory results [46–48]. The complexity of multiple factors plays an important role in their manufacturing: the proteins used, the amount, adjuvants, appropriate doses, among others, require time and tests that enable the development of the most adequate and effective vaccine for human use [14].

Coccidioidomycosis is a disease that significantly impacts the quality of life of those who suffer from it and puts at risk the health of susceptible groups of disseminated disease in areas of high prevalence in the continent. Further studies must be carried out to achieve a better understanding of the genetic features of the fungus, its behavior in the environment, and its interaction with the human immune system, thus enabling the development of new preventive and therapeutic options, which can significantly impact the incidence of the disease in endemic areas, as well as reducing the complications associated with coccidioidomycosis.

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Histoplasmosis: Musculoskeletal Manifestations

21

Luis Fernando Pinto Peñaranda

Epidemiology

Histoplasmosis is the most common fungal infection in the United States [1]. The causative agent is *Histoplasma capsulatum*, a thermally dimorphic fungus that exists as a hyaline spore in the environment and as a yeast at body temperature. It lives particularly in humid soil and especially in soil that contains bird and bat droppings. Two varieties are known: in North America, Central America, South America, Oceania, Asia, and Southeast Europe, the variety capsulatum (*H. capsulatum* var. *capsulatum*) has been described, while in Central and Western Africa the variety Duboisii (*H. capsulatum* var. *duboisii*) is found [2, 3].

The fungus is endemic in the United States, in the Ohio and Mississippi river valleys, especially in the states of Mississippi and Missouri, but also in Texas, Louisiana, Alabama, Oklahoma, Kansas, Iowa, Kentucky, and Tennessee. It is estimated that between 60% and 90% of people living in these areas have been exposed to the fungus at some point during their lifetime. In a prevalence study, Bradley et al. estimated an incidence of 3.4 cases/100,000 inhabitants over 65 years in this area of the country, and 6.1 cases/100,000 inhabitants in the Midwest [2, 3]. In Latin America, the fungus is endemic in several areas of Mexico, Central and South America, especially in the Orinoco, Magdalena, Amazonas, San Francisco, Parana, and La Plata river basins [2, 3]. The described risk factors are living in or traveling to endemic areas, exposure to soils aerosolized by strong winds, constructions, and excavations, contact with bird breeding sites, or visiting caves inhabited by bats [1–3].

Diseases that affect cellular immunity confer greater susceptibility to disseminated histoplasmosis, even after exposure to small inoculant [4]. The main conditions are the extremes of life [2], HIV/AIDS [5, 6], organ transplantation [7, 8], use of tumor necrosis factor inhibitors (TNFi) [9–11], and other immunosuppressants [12–14]. Worldwide, patients with HIV/AIDS, especially those who do not have access to anti-retroviral treatment, have a higher prevalence of histoplasmosis. In Latin America, histoplasmosis is one of the most frequent opportunistic infections in patients with AIDS and approximately 30% of those infected by the fungus die from it [4–6]. In organ transplantation recipients, infection by *H. capsulatum* may be due to transmission by the donor or reactivation of latent infection [7, 8].

In individuals treated with TNFi, histoplasmosis is the second opportunistic infection after tuberculosis and the first systemic fungal infection [9–11].

Histoplasmosis mortality is unknown, due to the fact that studies only include symptomatic and more severe cases. It is estimated that among patients hospitalized for the disease 4% of them die from it, 5% of children, and 8% of adults [4].

Microbiology and Life Cycle

Mycelia are found in the form of microconidia and macroconidia. The microconidia circulate in the air once the contaminated soil is removed. After inhaled, they are phagocytosed by alveolar macrophages where aided by body temperature, they are transformed into yeasts, which are the infectious form of the fungus [2]. Yeasts then multiply and are transported through the circulation and the reticuloendothelial system to the lymph nodes and to other organs [2, 7].

H. capsulatum infection depends on the immune status of the host [15–20] and the amount of inhaled microconidia. In most cases exposed individuals, especially those immunocompetent, do not experience symptoms or only present mild respiratory manifestations since the infection is controlled by cell-mediated immunity, particularly cytotoxic T cells [16, 17, 19, 20]. TNF-α plays a crucial role in controlling infection [15, 18].

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_21

Clinical Manifestations

Histoplasmosis is a clinically polymorphic disease, which may exhibit different manifestations, severity, organ involvement, and radiologic presentations. The disease is defined by the presence of suggestive symptoms (fever, weight loss, respiratory manifestations, lymphadenopathy, hepatomegaly, splenomegaly, and gastrointestinal manifestations) plus one of the following:

1. Positive culture
2. Demonstration of *H. capsulatum* in any tissue (cytology or biopsy)
3. Demonstration of urinary antigen in serum or urine (ELISA)
4. Positive serology (demonstration of H or M bands by immunodiffusion or titers greater than or equal to 1: 8 by complement fixation [2])

Several clinical syndromes are recognized which are not exclusive and may overlap. The diagnosis of pulmonary histoplasmosis requires the presence of radiologic findings, such as infiltrates and/or mediastinal adenopathies with or without the presence of symptoms [2, 4, 21].

Acute Pulmonary Histoplasmosis

Acute pulmonary histoplasmosis occurs after the inhalation of the microconidia; immunocompetent individuals are asymptomatic or have a self-limited form with non-specific "flu-like" symptoms [2, 4, 21].

In immunocompromised individuals, especially due to cellular immunodeficiency and in the extremes of life, an acute condition characterized by fever, chills, dry cough, and dyspnea may occur. Less frequently, mediastinal adenopathy, arthralgia, arthritis, erythema nodosum, and erythema multiforme that subside in approximately 2 weeks are observed. The X-ray shows patchy infiltrates, and the tomography exhibits hilar adenopathy. Elevation of liver tests and pancytopenia can be observed in laboratory exams [5–14].

It is common that the disease is misdiagnosed as viral infections or bacterial pneumonia at this stage. Less frequently it has been mistaken with sarcoidosis, reactive arthritis, serum sickness, and allergic reactions to medications.

Subacute Pulmonary Histoplasmosis

Subacute pulmonary histoplasmosis manifests as a slowly progressive disease that evolves in weeks to months with some mild but persistent respiratory symptoms, occasionally accompanied by constitutional complaints. Chest X-ray shows alveolar and interstitial focal opacities, along with hilar and mediastinal adenopathy [2, 4].

Chronic Pulmonary Histoplasmosis

In these cases, the disease has a course of months to years and affects more population with chronic lung diseases with tobacco abuse, chronic obstructive pulmonary disease, and pneumoconiosis, which induces a slow and progressive respiratory deterioration with periods of exacerbation [2, 4].

During the evolution, patients present fever, night sweats, weight loss, cough, and dyspnea. Chest radiography reveals chronic lung disease with calcified hilar and mediastinal lymph nodes, and various pulmonary findings such as diffuse infiltrates, interstitial fibrosis, consolidations, and cavitation. Thickening and pleural fibrosis may also be found [2, 4].

Pulmonary Nodules

This presentation is usually asymptomatic; the nodules are non-specific and should be characterized by histopathological study.

Mediastinal Histoplasmosis

Mediastinal histoplasmosis may present as adenitis, granulomas, or mediastinal fibrosis. Adenitis is distinguished by an increase in the size of the mediastinal lymph nodes, usually during acute infection. Granulomas usually present several decades after the acute infection; coalescing lymph nodes masses are formed with necrosis. Both adenitis and granulomas can manifest with cough, dyspnea, airway compression, and bacterial superinfection. Tracheoesophageal fistula or superior vena cava syndrome is uncommon and presents more in the granulomatous forms [2, 4]. Mediastinal fibrosis is very late stage and can be asymptomatic or compress structures such as the superior vena cava and the pulmonary artery, causing different clinical conditions.

Pericarditis

Pericarditis is a rare manifestation of acute histoplasmosis; it is usually inflammatory, without pericardial infection and is produced through irritation of the pericardium by an inflamed mediastinal nodule [4].

Progressive Disseminated Histoplasmosis

In subjects with impaired immunity, especially cellular, hematogenous dissemination of *H. capsulatum* may occur. The clinical picture can appear in the acute stage, immediately after the pulmonary infection occurs, or many years later, once the state of immunosuppression occurs, due to the reactivation of latent histoplasmosis [4].

Diagnosis of disseminated histoplasmosis is defined by the presence of clinical, microbiological, or radiologic extrapulmonary involvement. The clinical setting varies from a subacute disease with fever, nocturnal diaphoresis, cough, and slowly progressive dyspnea (including fever of unknown origin) to a sudden onset with systemic inflammatory response syndrome [4, 22, 23].

The fungus can infect any organ; the liver, spleen, lymph nodes, bone marrow, oral mucosa, central nervous system, and adrenal glands are the most common. Skin involvement is unusual, except in patients with HIV/AIDS [4–6, 24].

Histoplasmosis and Musculoskeletal Manifestations

Rheumatologic manifestations are exceptional. In an institutional series of 111 patients with disseminated histoplasmosis, Assi et al. did not find cases with musculoskeletal manifestations [21]. Similarly to the systemic forms, the musculoskeletal compromise is very extensive. Four groups of manifestations can be distinguished: the reactive form; the direct musculoskeletal infection (arthritis, tenosynovitis, myositis, panniculitis, osteomyelitis); the systemic infection by *H. capsulatum* resembling rheumatologic diseases; and superinfection in individuals treated with immunosuppressants, such as steroids, methotrexate, leflunomide, TNFi, and abatacept [25]. Figures 21.1 and 21.2 show Histoplasma panniculitis in two immunosuppressed patients, with dermatomyositis and systemic lupus erythematosus, respectively.

Reactive Arthritis

Rosenthal et al. [26] observed that 6% of the individuals infected by *H. capsulatum* during an epidemic in Indianapolis presented musculoskeletal manifestations, especially arthralgia or arthritis with periarticular erythema, with the involvement of large and small joints of upper and lower limbs. In half the cases, arthritis occurred during the initial infectious episode, and the others presented it between 2 and 10 weeks later; 50% of the patients presented erythema nodosum. This condition was characterized as reactive arthritis, since *H. capsulatum* was not detected in synovial fluid and biopsies studies, and less

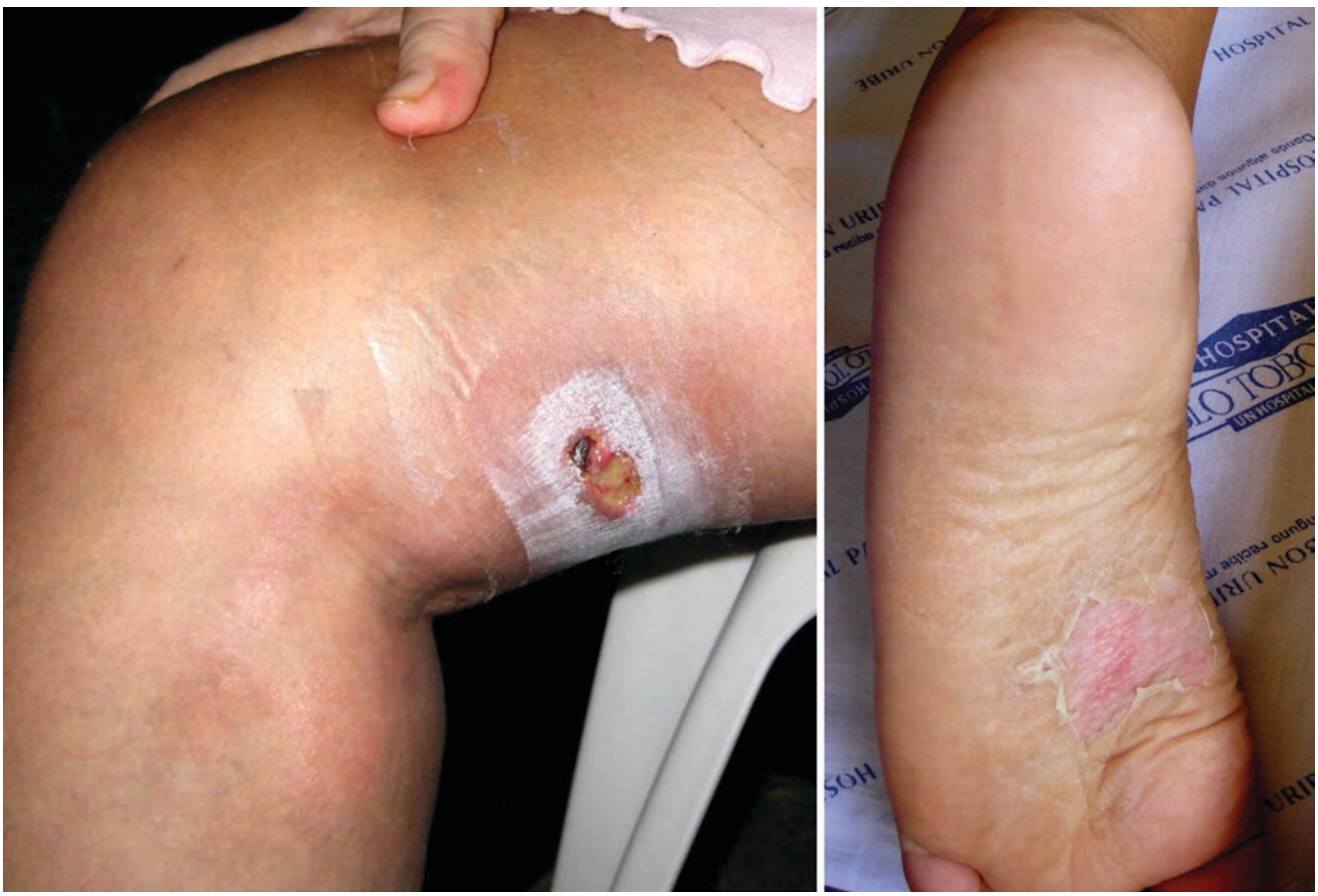

Fig. 21.1 Histoplasma panniculitis in a patient with dermatomyositis. (Courtesy Dr. María Cristina Trujillo MD. Dermatologist. Universidad Pontificia Bolivariana—Clínica Aurora. Medellín Colombia)

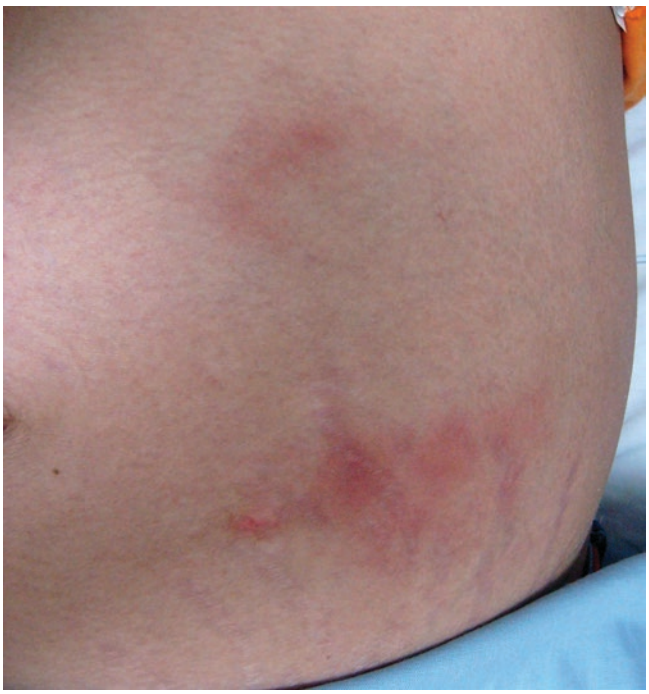

Fig. 21.2 Histoplasma panniculitis in a patient with Systemic lupus erythematosus. (Courtesy Dr. María Cristina Trujillo MD. Dermatologist. Universidad Pontificia Bolivariana—Clínica Aurora. Medellín Colombia)

than 1% of subjects had persistent symptoms. Likewise, Sellers et al. [27] observed the predominance of arthralgia or migratory arthritis of the lower limbs during an epidemic in Greenwood, South Carolina. During the primary infection, the most common rheumatologic manifestation is acute migratory polyarthritis resembling gonococcal arthritis, even though it may also be additive [26, 27].

Musculoskeletal Infection

In the case of monoarthritis, the knee is the most commonly involved joint; less frequently, the affection of the wrist and tarsus [28], finger flexor tenosynovitis, carpal tunnel syndrome [29, 30], and prosthetic joint involvement are described [31]. In these cases, the cause is the joint infection by *H. capsulatum* var. *capsulatum* and var. *duboisii*. Epiphyseal slip in children [32], as well as osteomyelitis in the radius, fibula, metatarsals, and cuneiforms, can occur [33–35]. Liu et al. described the case of an immunocompetent patient with spinal pain who presented lytic lesions in the T4 - T6 vertebrae with vertebral body compression and right lateral pedicle lysis, suggestive of metastatic disease. The biopsy showed granulomatous inflammation with necrosis, and demonstration of histoplasmosis [36]. Spinal disease may resemble tuberculous spondylodiscitis [37].

Systemic Infection by *Histoplasma capsulatum* Mimicking Autoimmune Diseases

Systemic manifestations of histoplasmosis can be misinterpreted as persistent activity or relapse of rheumatologic diseases, causing a delay in the diagnosis of infection. On the other hand, the initial symptoms of the infection can be confused with diseases such as systemic lupus erythematosus (SLE), Still disease, or systemic vasculitis [38].

General manifestations such as fever, arthralgia, arthritis, myalgia, fatigue, oral ulcers, adenomegaly, and dyspnea, as well as paraclinical findings such as cytopenias, alteration of liver tests, and pneumonitis are frequent in histoplasmosis and systemic autoimmune diseases. In immunosuppressed subjects with systemic rheumatologic diseases, unusual manifestations of disseminated histoplasmosis occur, with the involvement of the central nervous system, gastrointestinal tract, eyes, larynx, skin, mouth, and more rarely, the upper respiratory tract [39, 40].

In the Indianapolis epidemic, seven patients presented with arthralgia and hilar adenopathy and were diagnosed as sarcoidosis ("pseudosarcoidosis") [41]. The literature describes two cases of disseminated histoplasmosis in patients with rheumatoid arthritis (RA) with high rheumatoid factor titers, splenomegaly, and neutropenia, resembling Felty's syndrome [42]. Sen et al. illustrated the case of a patient with a history of psoriatic arthritis who presented polyarthritis of small joints with a negative rheumatoid factor, resembling relapse of the disease. This picture was followed by chronic monoarthritis with the destruction of the tarsal bones by *H. capsulatum*, initially interpreted as tarsitis associated with psoriatic arthritis [39].

Negri et al. [43] described several cases of unusual manifestations of histoplasmosis in patients with rheumatologic diseases, in whom the differential diagnosis between infection and complications of treatment or autoimmune disease was challenging:

- Patient with RA who presented pancytopenia with Coombs-positive autoimmune hemolytic anemia, hepatomegaly, splenomegaly, and demonstration of *H. capsulatum* in a nasal ulcer
- Patient with RA under treatment with methotrexate (MTX), leflunomide (LEF), and and prednisolone (PDN), who presented pneumonitis and chronic lingual ulcer in which *H. capsulatum* was isolated
- Patient with RA under treatment with MTX, LEF, and PDN with an atypical case of disseminated histoplasmosis to a single organ who presented flexor tenosynovitis of the third finger of the hand, with spontaneous fistulization and demonstration of the fungus
- Female with SLE with 10-year therapy including corticosteroids and chloroquine who presented perforation of the

nasal septum and hard palate with nasopalatine fistula in which *H. capsulatum* was evidenced
- Subacute disseminated histoplasmosis confirmed in a lingual ulcer in a woman with fever, alopecia, proximal muscle weakness and neck flexors, dysphagia, pancytopenia, and positive antinuclear antibodies

Several cases of oral and nasal lesions caused by *H. capsulatum* have been described in Argentina, Brazil, Colombia, India, Morocco, South Africa, and the United States. The majority have been nasal septum injuries, inflammation, bleeding, ulcers, necrosis, perforation, and lysis. Ulcers on the soft palate, lysis of the hard palate, sinusitis and destruction of paranasal sinuses, and endophthalmitis are less frequently described [38, 43–46].

Lehur et al. [45] illustrated the case of a patient with HIV/AIDS without treatment, from an endemic country, who presented fever, osteolysis, and collapse of the nasal septum with the presence of scars and bleeding, interstitial pneumonitis, and subsequent perforation of the hard palate with oral and nasal communication. Initially, this case could be confused with granulomatosis with polyangiitis, cocaine-levamisole-induced vasculitis, or leishmaniasis [47, 48].

Several reports of panniculitis have been described in patients with rheumatoid arthritis, dermatomyositis, and systemic lupus erythematosus. The location of the lesions is variable (forearms, popliteal, calves, vastus lateralis, legs, abdominal wall). In all cases, the biopsy showed mixed panniculitis (septal and lobular); in one case with necrosis, and identification of *H. capsulatum*. Focal myositis and fasciitis can also be found. The main differential diagnosis is erythema nodosum, which is typically located in the anterior part of the legs [43, 49–51].

Other rare manifestations outlined are pancytopenia in patients with RA treated with MTX [52], and a patient with muscle weakness and rash resembling dermatomyositis [53].

Systemic Infection by *Histoplasma capsulatum* Related to the Treatment of Rheumatologic Diseases

The main adverse event of the treatment of inflammatory diseases with biological drugs has been the increased risk of opportunistic infections, already augmented by endogenous immunosuppression involving these disorders, and exogenous immunosuppression induced by previously or concomitantly used medications [54, 57].

Histoplasmosis is the most common opportunistic fungal infection associated with the use of biological therapy, mostly with TNFi and especially infliximab. Almost 60% of the cases of histoplasmosis in individuals with RA reported in the United States have received biologics for an average time of 15 months, a reason why it is considered to be a recent infection; most suffer the disseminated form, and in some, the immune reconstitution syndrome is the cause of the clinical deterioration [58]. It is possible that the majority of cases of histoplasmosis associated with TNFi use are primary infections, since the reactivation of latent infection is rare, even in endemic areas.

Tumor necrosis factor alpha (TNF-α) plays a key role in the activation of macrophages that are essential in the host response against *H. capsulatum* [15–17, 19, 20, 59–63]. Infection is more frequent with monoclonal anti-TNFα antibodies (infliximab and adalimumab) than with etanercept, which is a fusion molecule that binds a soluble TNF receptor bound to immunoglobulin G [60, 61]. The reason for this difference is that anti-TNFα antibodies block soluble TNF-α, together with the monomeric and trimeric forms associated with cells, inducing apoptosis and complement-mediated lysis of monocytes and T lymphocytes. Etanercept has no effect on cell-associated TNFα, does not induce apoptosis of monocytes and T lymphocytes, and only blocks soluble trimeric forms of TNFα [60, 61]. Blockade of this cytokine inhibits the formation of granulomas and facilitates de novo infection by *H. capsulatum*, mycobacteria, and other opportunistic microorganisms [62].

Cases of histoplasmosis have been described in patients with RA, SLE, adult-onset Still disease, dermatomyositis, and systemic sclerosis in association with treatment with infliximab, etanercept, adalimumab, certolizumab, abatacept, MTX, azathioprine, LFM, and corticosteroids. To date, no cases associated with the use of golimumab, rituximab, tocilizumab, and tofacitinib have been described. In most series, histoplasmosis is the second most frequent granulomatous infection after tuberculosis [10, 11, 55, 56].

The Food and Drug Administration (FDA) monitors the safety data of TNFi through AERS (Adverse Event Reporting System), a system for reporting adverse events voluntarily by health professionals and consumers, but mandatory by drug manufacturers [57].

Wallis et al. analyzed data on granulomatous infections in individuals who received etanercept and infliximab reported in AERS between 1998 and 2002. Up to 2002, more than 233,000 patients had received infliximab and more than 113,000 etanercept. In 622 reports, 639 infectious adverse events were described, 556 with infliximab (approximate rate of 2239/100,000 patients/year), and 83 with etanercept (approximate rate of 74/100,000 patients/year). Between 41% and 66% were treated with steroids and 41–43% with MTX concomitantly at the time of infection [55]. Most of the infections reported in AERS were tuberculosis with a rate of 144/100,000 patients-year with infliximab, and 35/100,000 patients-year with etanercept. There were 39 cases of histoplasmosis with infliximab (rate of 16.7/100,000 patients-year) and three cases with etanercept (rate of 2.7/100,000

patients/year) with etanercept; rate ratio: 6.3; $p < 0.001$. Granulomatous infections occurred earlier in patients receiving infliximab compared to those with etanercept (average 40 vs. 236 days; $p < 0.001$); 70% of the cases associated with infliximab and 28% of the cases associated with etanercept occurred in the first 90 days of treatment ($p < 0.001$) [55].

Winthrop et al. [56] published the results of a survey on serious infections presented by patients treated with TNFi and other biological therapies approved until 2007, in which 48.9% of the members of the Emerging Infection Network-Infection Diseases Society of America participated. They reported 1876 mycobacterial infections, 54% (1021) non-tuberculosis and 46% (855) tuberculosis. Less frequently, they found invasive infections by Staphylococcus aureus (73 cases), histoplasmosis (56 cases), Streptococcus pneumoniae severe infections (20 cases), cytomegalovirus (18 cases), aspergillosis (16 cases), parasites (10 cases), and other infections (between 2 and 5 cases—listeriosis, legionellosis, blastomycosis, coccidioidomycosis, and salmonellosis).

Tsiodras et al. [64] presented the results of a systematic review of the literature published between 1966 and 2007, searching for fungal infections associated with the use of infliximab, etanercept, and adalimumab. The most frequent fungal infection was histoplasmosis, with 30% of the cases (84/281); 86% (72) of the cases were related to infliximab, 10% (8) with etanercept, and 5% (4) with adalimumab; 77% (216) of the subjects had RA and 23% (65) inflammatory bowel disease. The clinical picture described in most of the individuals was the classic one characterized by fever, malaise, cough, dyspnea, and interstitial pneumonitis. In the majority of cases, histoplasmosis was pulmonary, and subsequently hepatic, intestinal, disseminated, and cutaneous (panniculitis). Histoplasmosis cases occurred earlier in patients that received infliximab (median of 55 days; IQR: 15–140) than in those treated with etanercept (median 144 days; IQR: 47–240) and took place after three infliximab infusions (IQR: 2–4).

Olson et al. [65] characterized the manifestations and risk factors for histoplasmosis in patients with RA in an endemic region in the TNFi era. In the Mayo Clinic database, they found 26 cases of histoplasmosis between 1998 and 2009. Ninety-six percent (25) of the subjects received traditional disease-modifying antirheumatic drugs (DMARDS), 81% (21) MTX, 58% (16) prednisolone, 19% (5) LFM, and 19% (5) hydroxychloroquine; 58% (16) of the individuals received TNFi at the time of infection: 27% (7) adalimumab, 23% (6) infliximab, and 8% (2) etanercept. The time between the onset of TNFi and the diagnosis of histoplasmosis was variable (average: 15 months; 2–32), and the delay between the onset of symptoms and the diagnosis of histoplasmosis was less than 4 weeks in 54% of cases, between 5 and 10 weeks in 38%, and greater than 10 weeks in 8% of them.

The most common clinical manifestation was fever that occurred in 73% (19) of the patients; in 54% of the cases (17), the lung was the only site of infection, while 35% (9) suffered lung involvement and subsequent spread to the liver, spleen, intestine, and bone marrow, and 11% (3) suffered disseminated infection without lung affection. Radiologic findings included focal pneumonitis, pulmonary nodules, hilar and mediastinal lymphadenopathies, as well as alveolar infiltrates. Serology was positive in 88.4% of the assessed cases (23/26), the urinary antigen in 54% (13/24), and the cultures (sputum, bronchoalveolar lavage, lung tissue, blood, bone marrow, intestine, peritoneum) in 62.5% (15/24). Histological studies demonstrated *H. capsulatum* spores in the lung, bone marrow, liver, and small intestine.

Vergidis et al. [66] described a retrospective cohort of 98 cases of histoplasmosis complicating therapy with TNFi and other immunosuppressants, diagnosed at 20 high-complexity centers in the United States, mainly located in endemic areas for the disease; 53.1% (52) of the patients had a diagnosis of RA, 38.1% Crohn's disease, 7.2% psoriasis and, less frequently, ankylosing spondylitis, Takayasu arteritis, sarcoidosis, and uveitis. The diagnosis of histoplasmosis was established between 1 and 88 months (median: 15 months), after initiating TNFi. In this group of subjects, pulmonary affection was successive, most developed in the disseminated form and rare manifestations such as arthritis and cutaneous involvement were presented. Table 21.1 presents the organs involved.

The disease was severe in 17.3% (17) of the cases, moderate in 56.1% (55), and mild in 26.5% (26). The concomitant use of corticosteroids (OR 3.94; 95% CI: 1.06–14.6; $p = 0.04$) and the highest levels of urinary antigen (OR 1.14; 95% CI: 1.03–1.25; $p = 0.008$), neither the underlying disease nor the TNFi type, were associated with the severity of histoplasmosis. The mortality attributed to histoplasmosis was 3.2%.

Table 21.1 Organ involvement in 98 patients with histoplasmosis associated with the use of TNFi

Affected organ	% (*n*)
Lung	79.6 (79)
Disseminated disease	75.5 (75)
Circulatory system (fungemia)	18.4 (18)
Liver	15.3 (5)
Spleen	15.3 (15)
Bone marrow	14.3 (14)
Gastrointestinal tract	12.2 (12)
Lymph nodes	7.6 (5)
Musculoskeletal system	4.1 (4)
Skin	3.1 (3)
Central nervous system	2 (2)
Adrenal glands	2 (2)
Paranasal sinuses	1 (1)
Epiglotitis	1 (1)

Data from: Vergidis et al. [66]

Infliximab was the biological utilized in 67.3% (66) of these individuals, followed by adalimumab in 23.5% (23), and etanercept in 9.2% (9) of them. The majority of patients received other immunosuppressants at the diagnosis of histoplasmosis: MTX 43.9% (43), corticosteroids 33.7% (33), azathioprine 13.3% (13), 6-mercaptopurine 6.1% (6), and LFM 1% (1); 28% (28.6) were taking two immunosuppressants.

In this series, 9.2% of the individuals (9) had worsening respiratory symptoms, some acute respiratory distress syndrome (ARDS), increased number and size of lymphadenopathies, and abnormal liver enzymes, between 1 and 45 weeks (median 6: weeks) after TNFi discontinuation. This clinical picture was interpreted as inflammatory immune reconstitution syndrome (IRIS). The majority of subjects had received infliximab and progressed to disseminated histoplasmosis, three of them were treated with corticosteroids and all recovered without sequelae [66].

IRIS has developed after TNFi suspension upon confirmation or suspicion of histoplasmosis; it is a paradoxical clinical worsening, even in the presence of microbiological improvement and is characterized by reappearance or worsening of fever and dyspnea that may even present with diffuse alveolar damage and require mechanical ventilation. Other manifestations described are hepatitis, pancytopenia, and macrophage activation syndrome. The clinical scenario can be interpreted as worsening of the infection, which causes a delay in the diagnosis; it is suggested to suspect IRIS in case of persistence or reappearance of fever and clinical deterioration in patients who receive intense antifungal treatment and who improve with steroids [63, 67, 68].

Before initiating treatment with TNFi, it is suggested to investigate some risk factors such as travel or residence in areas of endemicity for *H. capsulatum*, occupational contact with birds or caves, pneumonia in the previous 2 years, or history of histoplasmosis. However, there are no recommendations on routine X-ray screening or *H. capsulatum* antibodies or antigen detection in subjects who will receive these medications [69].

Laboratory Diagnosis

The gold standard for diagnosis of histoplasmosis is the demonstration of yeasts in tissues and/or their isolation in culture or body fluids; however, there is not always access to these specimens for which serological tests, antigen detection, and molecular biology technique are employed [4, 22, 69–72].

The sensitivity and specificity of these tests vary in different clinical situations and tissues. In suspected cases of histoplasmosis, ≥2 blood cultures for fungi, antigenemia, antigenuria, and serology should be requested. If these tests show negative results, it is recommended to perform bronchoscopy with biopsies and bronchoalveolar lavage (BAL) to search for the antigen, culture, cytology, and pathology study. Finally, if *H. capsulatum* is not detected with the previous tests, biopsies should be taken from the compromised sites [4].

The Council of State and Territorial Epidemiologists (CSTE) publishes its case definition to homogenize the detected subjects and improve the epidemiological surveillance of histoplasmosis. The new case criteria require clinical, laboratory, and epidemiological evidence of the disease in people who have never suffered it or who have spent at least 24 months since the previous diagnosis of histoplasmosis in the same patient [73].

According to The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infection Diseases Mycosis Study Group (EORT/MSG), the proven diagnosis of invasive fungal infection requires verification by culture or histopathology. If cultures are not available or negative, the presence of compatible clinical symptoms compatible, one or more predisposing conditions, and mycological evidence (e.g., antigenuria) is considered a probable case [74].

Culture and Histological Stains

H. capsulatum stains poorly with Gram, so it is only rarely detected with this technique. Calcofluor White Stain is more useful for detecting it in biological specimens because it binds chitin in the cell wall of the fungus [2, 4, 72, 75–77].

Cultures are more useful in severe and disseminated forms, and any tissue or body fluid can be employed. Solid culture media, such as Sabouraud Dextrose Agar, incubated between 25 °C and 30 °C allows the growth of the fungus within 2 and 3 weeks, yet it can take up to 8 weeks. Once the colonies are identified, the lactophenol cotton blue test was applied to determine the morphology of the mycelia, which depends on its maturity: initially septate hyphae, followed by 2–5 μm microconidia, and finally 7–17 μm tuberculated macroconidia. The incubation at 37 °C induces the transformation of mycelia to yeasts. Other fungi also have macroconidia as structural forms; thus, more specific identification tests are required once cultivated. Nowadays, rapid molecular tests are applied for this. The demonstration of *H. capsulatum* in tissues confirms the diagnosis but does not imply active histoplasmosis. In lung or mediastinal granulomas, non-viable organisms can be identified even years after the acute infection. In these cases, incomplete granulomas and fibrosis are observed, and the cultures are negative [2, 4, 72, 75–77].

Typically, *H. capsulatum* yeasts are ovoid, narrow-based, and are mainly seen inside macrophages and histiocytes or forming clusters, but can be extracellular. *H. capsulatum* var.

capsulatum yeasts measure 2–4 μm, and those of *H. capsulatum* var. *duboisii* measure 6–12 μm. The most useful stains to identify *H. capsulatum* are Gomori Methenamine Silver (GMS) and Periodic Acid Schiff (PAS). Hematoxylin & eosin staining is of little use for this purpose, except when there is a large load of the microorganism. For the differential diagnosis with other germs, specific histochemical stains should be used. The histopathological differential diagnosis is wide, including *Cryptococcus* spp., *Blastomyces dermatitidis*, *Candida glabrata*, *Pneumocystis jirovecii*, *Coccidiodes* spp., *Talaromyces marneffei*, Leishmania, *Toxoplasma gondii*, and *Trypanosoma cruzi* [4, 72, 75–77].

Mucicarmine is linked to *Cryptococcus* spp. capsule, generating the halo sign that enables differentiation from *H. capsulatum*. If it is not encapsulated, the presence of Cryptococcus melanin can be detected with the Fontana-Masson stain. *Candida glabrata* has the highest overlap with *H. capsulatum* in histological specimens. *H. capsulatum* yeasts are homogeneous in shape and size, have intracellular localization, and exhibit granulomatous inflammatory response. *C. glabrata* is located at the extracellular level; the shape and size of the yeasts are heterogeneous, with a suppurative histological response. *Pneumocystis jirovecii* stains with PAS and GMS but not with mucicarmine, since it is not encapsulated, *Toxoplasma gondii* and *Trypanozoma cruzi* do not stain with PAS and GMS but do so with hematoxylin & eosin [4, 72, 75–77]. Figures 21.3 and 21.4 show liver granulomas stained with hematoxylin and eosin, containing *H. capsulatum*. Figures 21.5 and 21.6 show liver biopsy stained with silver methenamine containing *H. capsulatum*.

The characteristic pathological finding is the presence of non-caseating granulomas, in which *H. capsulatum* is identified with GMS or PAS stains. In healed granulomas or calcified ganglia, the presence of spores can be observed, which does not necessarily mean active disease. The most commonly used specimens to detect the fungus are sputum, BAL, blood, bone marrow, lymph nodes, and, less frequently, solid organs [4].

Cytology samples obtained from solid tissues, ganglia, or body fluids have less sensitivity than those obtained by biopsy and provide rapid presumptive evidence of histoplasmosis. Similarly to tissue biopsies, narrow-based ovoid yeasts, mostly phagocytized by macrophages, are observed with PAS and GMS stains. The sensitivity of BAL in cytology is 50% but can be increased to 97% if used in combination with antigen tests [4, 78].

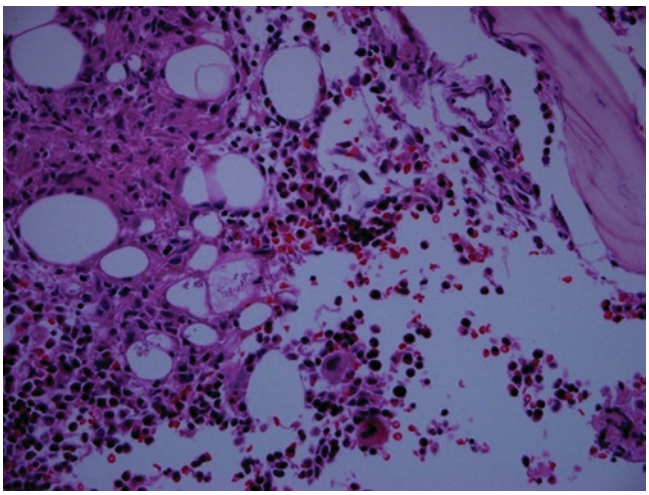

Fig. 21.4 *Histoplasma capsulatum* in liver biopsy. Hematoxylin & Eosin ×100. (Courtesy Dr. Alejando Velez and Juan Camilo Perez Pathologists MD. Hospital Pablo Tobón Uribe. Medellín Colombia)

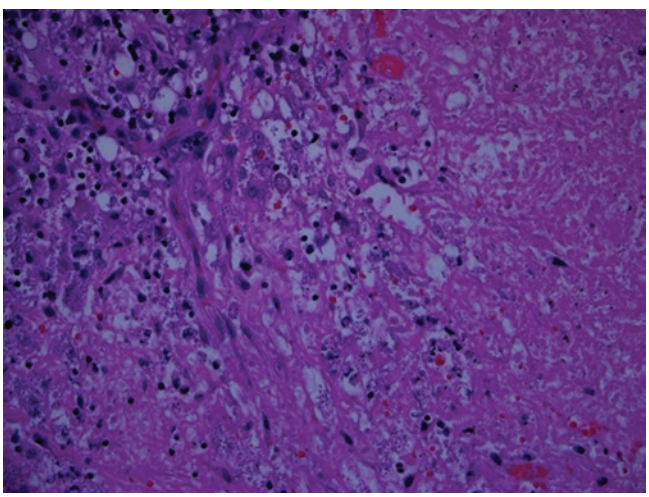

Fig. 21.3 *Histoplasma capsulatum* in liver biopsy. Hematoxylin & Eosin ×40. (Courtesy Dr. Alejando Velez and Juan Camilo Perez Pathologists MD. Hospital Pablo Tobón Uribe. Medellín Colombia)

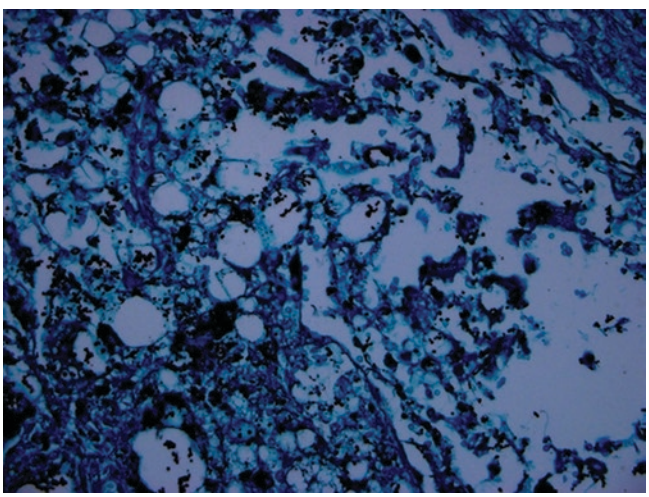

Fig. 21.5 *Histoplasma capsulatum* in liver biopsy. Silver methenamine ×40. (Courtesy Dr. Alejando Velez and Juan Camilo Perez Pathologists MD. Hospital Pablo Tobón Uribe. Medellín Colombia)

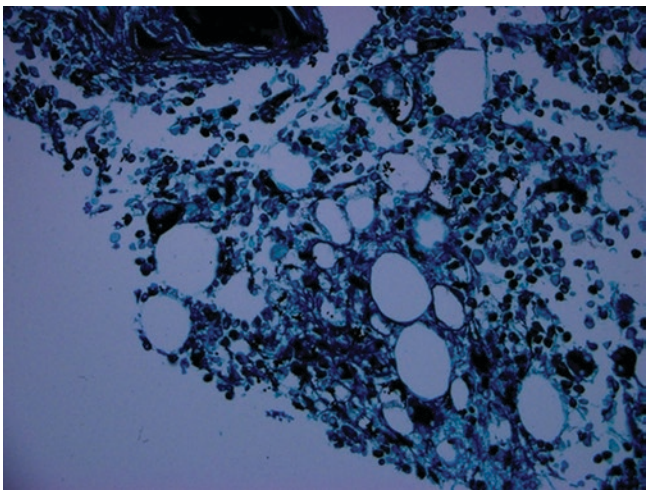

Fig. 21.6 *Histoplasma capsulatum* in liver biopsy. Silver methenamine ×100. (Courtesy Dr. Alejando Velez and Juan Camilo Perez Pathologists MD. Hospital Pablo Tobón Uribe, Medellín Colombia)

Antigenic Detection

The most sensitive and utilized method for diagnosing disseminated and acute pulmonary histoplasmosis is through the detection of serum and urine *H. capsulatum* antigen detection in serum and urine. It is a non-invasive, highly sensitive and easily interpretable method that is applied to make a probable and rapid diagnosis of histoplasmosis, in subjects with risk factors and a clinical picture compatible with the disease. Due to their quantitative nature, third generation immunoenzymatic techniques (EIA) are useful for patient follow-up, since the titers decrease with the favorable response to treatment and rise when there is a relapse or therapeutic failure. The sensitivity of this technique depends on the clinical presentation: 91.8% in the disseminated form, 87.5% in the chronic pulmonary scenario, 83% in the acute pulmonary, and 30% in the subacute forms [79–81].

H. capsulatum antigen detection is more sensitive in urine but can be done in serum, cerebrospinal fluid (CSF), BAL, and other body fluids. In order to increase sensitivity, it can be performed simultaneously in urine and serum in specific situations, such as CNS and isolated lung involvement, and should be sought at specific sites. An important limitation is its cross-reactivity with other fungal antigens, such as *Paracoccidioides brasiliensis*, *Coccidioides immitis*, *Coccidioides posadasii*, and *T. marneffei* what diminishes its specificity. MiraVista *H. capsulatum* Galactomannan EIA is the test that shows greater sensitivity and specificity in several surveys. An alternative is IMMY ALPHA Histoplasma EIA with use of Analyte-specific-reagent (ASR) [79–81].

Serological Tests

Detection of *H. capsulatum* antibodies is useful in subacute and chronic forms of the disease, when antigen detection is negative or suboptimal, but is not useful for the diagnosis of acute infection, because it takes 4–8 weeks to be detectable. On the other hand, serology is not helpful to monitor the response to therapy, since the titers decline slowly, and sometimes incompletely [4, 82–85]. The three most common tests are complement fixation (CF), immunodiffusion, and EIA.

Immunodiffusion detects antibodies that precipitate on agar gel after binding with the H or M *H. capsulatum* antigens. In 80% of subjects with acute histoplasmosis, the M-band is detected; however, it does not distinguish acute, latent, or past infection, as it persists for long periods, whereas only 20% of those suffering chronic infections have a positive H-band, which is more useful for establishing acute infection. In general, H-precipitins are further associated with active infection than H-bands. Titers ≥1:8 by CF indicate prior exposure to *H. capsulatum*; titers ≥1:32 or with an increase of ≥4 times the previous titer are strongly suggestive of acute infection [4].

In general, CF is more sensitive than immunodiffusion (90 vs. 80%), but less specific, both can cross-react with tuberculosis, sarcoidosis, and other fungal infections. The appearance of complement-fixing antibodies can take up to 6 weeks. Less than 5% of people, including residents in endemic areas, are seropositive for *H. capsulatum* by CF or immunodiffusion. EIA is more sensitive but less specific than the other serological tests since it has a high false-positive rate [82–85].

In CSF, the detection of antibodies by CF or immunodiffusion is more sensitive than the culture and is considered sufficient for the diagnosis of *H. capsulatum* meningitis. In individuals with deficiencies of humoral immunity, the serological response to the fungus is decreased, but in those treated with TNFi the serological response is present [82–85].

The presence of antibodies indicates that the subject has been exposed to *H. capsulatum* in the past and indicates acute infection in the following situations:

Detection in serum:

1. Titer elevation ≥4 times by CF
2. Detection of the H band by immunodiffusion
3. Demonstration of previously negative M band by immunodiffusion

Detection in CSF:

1. Titers ≥1:32 by CF
2. Demonstration of previously negative M band, by immunodiffusion

The combination of various detection techniques can improve diagnostic performance. For example, combining serological tests with antigen detection significantly increases sensitivity for the diagnosis of acute pulmonary histoplasmosis. These strategies can be used in immunocompromised patients with decreased humoral response in whom serological tests are less sensitive [86].

Molecular Methods

Although the gold standard for the diagnosis of histoplasmosis is culture, molecular techniques can be applied. To date, the studies are small and their results are not generalizable. At present, the greatest use of molecular methods is the implementation of a rapid DNA test to fungi isolated in culture. Polymerase chain reaction (PCR) assays have been developed, employing a large number of molecular targets, and offer two advantages: rapidity for diagnosis and high specificity; however, they are not yet approved by the FDA [87–89].

In situ tissue hybridization techniques, especially in blood or cultures, have shown a good performance in the fungus DNA detection. FISH (fluorescent in situ hybridization) detects *H. capsulatum* rRNA in blood cultures and can avoid the need for colonies growth to obtain the definitive diagnosis [4, 87–89].

Treatment of Histoplasmosis

Prevention consists basically of avoiding risk activities and contact with birds and bats droppings [2]. Prophylaxis is indicated only in cases of epidemic outbreaks with rates above ten cases per 100,000 patients/year and should be continued until the outbreak subsides [58]. In subjects with histoplasmosis diagnosed 2 years prior to the onset of TNFi, or with suggestive radiological or serological findings, some authors propose to administer itraconazole 3 months before initiating the biologic and continuing for 1 year [58]. In individuals who receive immunosuppressants due to inflammatory diseases, organ transplantation, cancer, and who have chest radiography or serology indicative of previous histoplasmosis, the usefulness of prophylaxis has not been demonstrated.

Mild acute pulmonary histoplasmosis can be self-limiting without requiring treatment in the immunocompetent population [90]. Acute moderate to severe pulmonary, disseminated and CNS involvement require management with amphotericin B and itraconazole. In highly suspicious cases, it is recommended to start empirical treatment until the results of the diagnostic tests are available [69].

Untreated disseminated histoplasmosis is usually fatal. Mild cases can be treated with itraconazole from the beginning, but in severe cases it is necessary to initiate amphotericin B, especially in liposomal form, which has greater tissue penetration, less renal toxicity, and infusion reactions. After 1–2 weeks with amphotericin B (4–6 weeks for CNS histoplasmosis), the treatment with itraconazole can be consolidated [69, 90, 91].

In most cases, a minimum duration of treatment is recommended for 1 year and until the antigenemia is less than 4 ng/mL, but in immunocompromised subjects in whom immunosuppression cannot be reversed, treatment should be indefinite with periodic monitoring of itraconazole levels. In individuals with HIV/AIDS, treatment withdrawal can be considered when the T lymphocyte count is greater than 150 CD4/uL, viral load less than 50 copies/mL, antigenemia less than 2 ng/mL, and absence of CNS histoplasmosis. During treatment, it is advocated to follow the Histoplasma antigen in serum and urine [69, 90].

In subjects with autoimmune rheumatologic diseases, questions arise as to which patients the treatment of histoplasmosis is indicated if immunosuppressive drugs can be restarted, when to do so, and if TNFi therapy can be restarted at any time. There are no clear guidelines that answer these questions.

According to the IDSA (Infectious Disease Society of America) criteria, patients with autoimmune rheumatologic disorders should be treated and are recommended itraconazole 200 milligrams tid for the first 3 days, followed by 200 milligrams bid for 12 months if histoplasmosis is mild to moderate. For moderate to severe cases, it is recommended to start with liposomal amphotericin B 3–5 milligrams/kg/day for 1–2 weeks, followed by itraconazole [69, 92].

Some authors suggest that treatment may be discontinued after 1 year in patients who will not restart TNFi, while those who receive it should continue itraconazole for as long as they are treated with the biologic. Smith et al. restarted treatment with TNFi in 33.8% (25) of their patients but did not specify how many of them had RA.61 The FDA recommends definitively suspending treatment with TNFi with a presumptive or definitive diagnosis of systemic fungal infections [57].

The ISMIR group (Italian Group of Study and Management of the Infections in patients with Rheumatic Diseases) suggests TNFi withdrawal in case of histoplasmosis and strictly monitor the presentation of IRIS and restart the non-biological DMARDs after a minimum treatment time of 12 months, if the urinary antigen is negative and there are no signs of residual disease. They propose that in areas of endemicity for Histoplasma, chest X-rays and screening with urinary antigen should be done before initiating TNFi, and follow-up with antigenuria every 3–4 months [93]. The non-biological immunosuppressive drugs could be reinitiated after 12 months of therapy if the antigenuria is negative and there is no clinical evidence of residual disease [4, 69, 92].

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Blastomycosis Arthritis

22

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Introduction

Blastomycosis is a rare systemic fungal infection caused by the thermally dimorphic fungus *Blastomyces dermatitidis*, which is endemic in forested areas of the United States and Canada. This fungus is generally found around large lakes and along the Mississippi and Ohio river valleys, although cases have also been described in other parts of the world [1–3]. Usually, the disease affects the lungs, skin and other soft tissues; however, within fungal diseases, blastomycosis shows a special predilection for bone. This microorganism can cause arthritis directly by hematogenous spread or through contact with an affected bone [4]. When a diagnosis is made in a timely manner, bony and articular blastomycosis responds favorably to antifungal drugs with or without surgical debridement. The key to timely diagnosis is to maintain a high index of suspicion and a low clinical threshold to obtain appropriate microbiological samples [1].

Case Definition

Patients with blastomycosis frequently show joint symptoms; however, arthritis is rarely documented through synovial fluid analysis. Reports of joint involvement are unusual, and joint involvement has only rarely been described as the initial presentation of a disseminated disease [5]. Cases of mono-, oligo- or polyarthritis due to blastomycosis have been reported as the form in which the disease first presents [5–7]. Arthritis is defined as pain, limitation in the range of motion and synovial effusion in a joint. Additionally, the diagnosis of joint infection by blastomycosis usually requires a positive culture from synovial fluid or microscopic evidence of yeast in the synovial fluid, plus another positive culture from elsewhere in the body [5].

Epidemiology

The vast majority of confirmed cases of blastomycosis come from the United States and Canada, although cases have also been reported in Africa, Asia, Europe and Latin America [8–13]. The disease is endemic in the southern regions and in the northern part of the central United States. The main affected areas in North America are the Mississippi and Ohio River valleys as well as Manitoba, Ontario and around the Great Lakes. In general, blastomycosis is a rare disease. However, it does not require mandatory national reporting in all states. In states that do have mandatory reporting, the annual incidence rates range from approximately one to two cases per 100,000 inhabitants. Wisconsin has the highest incidence rate, ranging from 10 to 40 cases per 100,000 people per year in several northern counties [14, 15]. It is estimated that three to six cases requiring hospitalization per one million inhabitants occur annually in endemic areas [16].

Bone and joint symptoms are common in patients with blastomycosis, although true arthritis is much less frequent. In several large case series, bone involvement has been present in approximately 25–60% of patients with disseminated blastomycosis. The actual incidence of joint blastomycosis is unknown, although it is estimated to range from 3% to 8% [5, 13, 17].

Etiological Pathogenesis

The microorganism normally exists in the mold phase in the environment. Conidia of the fungus are aerosolized during activities that involve the movement of soil or decaying vegetation. Infection is acquired mainly after inhalation of the fungus, although infection by direct inoculation after trauma

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_22

may also occur [18]. In the lungs, inhaled conidia that evade the innate immune response, such as through phagocytosis mediated by macrophages and neutrophils, move to the yeast phase causing a respiratory infection [1, 18].

The initial innate immune response and subsequent cell-mediated immune response produce a granulomatous tissue response that can be seen in the lungs, skin and other organs. After conversion to the yeast phase, the microorganism can be disseminated hematogenously [18].

With respect to joint involvement that can occur in this disease, two possible mechanisms of fungal invasion have been proposed. Direct invasion leading to osteomyelitis from the spread of a contiguous focus of infection is clearly recognized, but it is also postulated that the fungus can enter joints through hematogenous spread [4, 19].

Clinical Manifestations

The most frequent clinical manifestation of infection by *B. dermatitidis* is lung infection, which occurs asymptomatically in approximately 50% of cases. In most cases, the disease manifests as a mild, self-limiting lung infection that occurs 2–3 weeks after exposure to the pathogen. Patients who are ill enough to seek medical attention are treated with antibiotics for an alleged community-acquired pneumonia. The most common presenting symptoms of pulmonary blastomycosis are cough, fever, night sweats, weight loss, chest pain, dyspnea, myalgias and hemoptysis. Chest x-ray may show areas of pneumonitis, mass-type infiltrates or nodules; hilar or mediastinal lymphadenopathies are observed rarely. Although the infection can be self-limiting, it is now recommended to treat all symptomatic persons in whom the diagnosis has been made to prevent progression to disseminated disease [20].

Chronic presentation forms are indistinguishable from tuberculosis or lung carcinoma [21]. Rarely, patients with pulmonary blastomycosis can develop acute respiratory distress syndrome (ARDS), which has been reported in both immunocompromised patients and previously healthy people. The diagnosis of blastomycosis is often delayed in many of these cases and is associated with a high mortality despite receiving the appropriate treatment [20].

The microorganism *B. dermatitidis* can spread to many different organs; the skin, bone and genitourinary systems are the most frequently affected. Early dissemination occurs in a large proportion of patients, although most remain asymptomatic. When extra-pulmonary manifestations appear, chest x-ray may remain normal or show only a residual process. Skin lesions often appear on exposed areas of the head, neck and extremities. The typical lesion appears as a crusted verrucous plaque with central microabscesses, although nodules, ulcers and pustules have also been described. There are usually multiple cutaneous lesions [22].

Involvement of the genitourinary tract occurs more frequently in men, with the prostate being the most commonly affected organ. Typical symptoms include dysuria and an obstructive syndrome. The central nervous system may also be affected, especially in immunocompromised individuals [20]. Most cases of blastomycosis occur in adults, although pediatric cases have also been reported—the diagnostic delay appears to be even more frequent in these patients [23].

Among fungal diseases, blastomycosis appears to have a special predilection for bones [4]. Bone is the third most frequent site where blastomycosis lesions are found, after the lungs and skin [24]. Most of the information available regarding bony blastomycosis comes from a small series of cases. Up to half of the cases of disseminated blastomycosis can show bone involvement. Any bone can be affected, including the vertebrae, ribs, bones of the face and skull, long bones, short bones, pelvic bones and shoulder blades. Patients with blastomycosis osteomyelitis have pain and local edema, which are frequently associated with an ulcer or an adjacent skin abscess.

Furthermore, synovial joint involvement has also been reported. The occurrence of arthritis via direct extension of osteomyelitis acquired from an adjacent focus of infection is well-documented, but cases of arthritis have also been recognized in the context of disseminated disease or as the only form of clinical presentation. Approximately 90% of patients with arthritis due to blastomycosis have extra-articular manifestations at the time of consultation [1, 5]. Arthritis is usually monoarticular, mainly affecting the knee, ankle or elbow. The pain is usually severe and acute, leading patients to consult a physician within a week following onset [5]. Vertebral blastomycosis is frequently associated with epidural, paravertebral or psoas abscesses [18].

Diagnosis

Given that the clinical manifestations of blastomycosis are nonspecific, it is necessary to maintain a high index of suspicion in order to achieve a timely diagnosis. Even in endemic areas, it is common for diagnosis to be delayed [24]. A detailed clinical history should include an individual's place of residence and history of travel to endemic areas, outdoor activities and exposure to plant material as possible risk factors. Immunosuppressed patients are at higher risk of suffering the disease [25, 26]. A history of blastomycosis in a feline or canine pet can also be clinically useful [20, 27]. Serological tests, as well as tests based on immunodiffusion and complement fixation, are not useful in blastomycosis due to their low sensitivities and specificities [20].

The diagnosis of blastomycosis can be made by demonstrating characteristic budding of broad-based, thick-walled

yeast cells upon direct examination of a body fluid (Fig. 22.1). Identification of a neutrophilic infiltrate with non-caseating granulomas in a tissue sample may suggest blastomycosis, and a detailed microscopic examination should subsequently be performed to determine the presence of yeasts of *B. dermatitidis*. In all cases, a microscopic diagnosis should be confirmed by culture to obtain a definitive diagnosis. The cultures require specialized media, and growth can take up to 4 or 5 weeks to be observed [22].

Examining urine samples with a *Blastomyces* cell wall antigen has shown lower diagnostic performance than expected and should not be used to rule out a diagnosis in patients with negative results but clinical suspicion [28]. This test is also not specific since there is cross-reactivity with histoplasma, paracoccidioidomycosis and penicilliosis [22]. Serial measurement appears to be useful for the evaluation of response to treatment or progression of the disease. After the initiation of treatment, an increase in antigenuria can be observed as a reflection of the excretion of dead fungal cells, followed by a progressive decrease in titers as a reflection of successful therapy [28].

There is no typical radiographic pattern of osteoarticular blastomycosis. X-ray may sometimes appear normal. Both long and short bones can be affected in a pattern that can be focal or diffuse. The most common findings are lytic "punched out" lesions and synovial effusions. Up to one-third of patients may show findings consistent with adjacent osteomyelitis [13]. Nuclear magnetic resonance imaging of the spine may show discitis, vertebral body destruction and paraspinal abscesses [29].

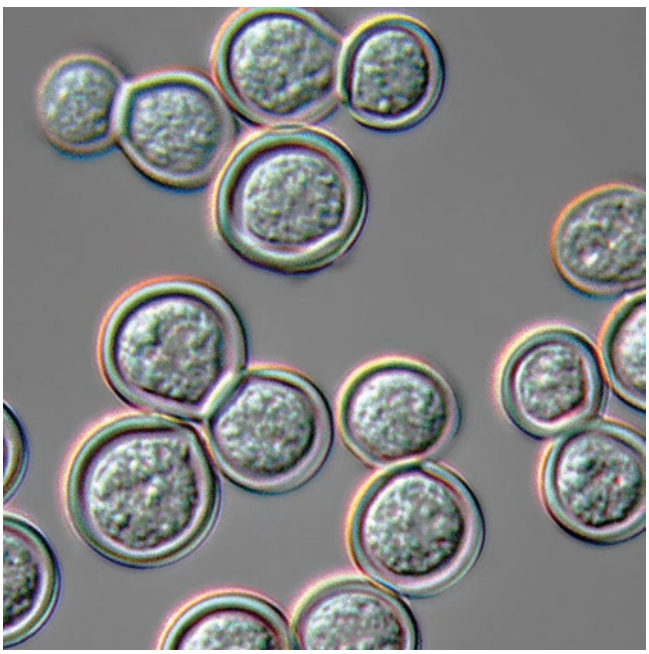

Fig. 22.1 Yeast form of *Blastomyces dermatitidis*. (From Wikimedia Commons. Creative Commons CC0 1.0 Universal Public Domain Dedication)

Treatment

Blastomycosis usually remains localized in the lungs; however, up to 40% of infected persons may develop extrapulmonary infection with cutaneous, osteoarticular, genitourinary or neurological involvement. In an immunocompetent host, pulmonary blastomycosis is usually mild and self-limiting and may not require treatment. However, it is recommended that all infected persons receive treatment to prevent extrapulmonary spread of the disease [20]. All people with moderate to severe pneumonia or disseminated infection or with pre-existing immunodeficiency should receive antifungal therapy [30].

In general, for the treatment of mild to moderate cases, an azole agent—especially itraconazole—may be used for 6–12 months. For cases of severe pulmonary or disseminated disease, central nervous system involvement or in immunocompromised patients, initial treatment with amphotericin B is recommended, followed by itraconazole upon the observation of a satisfactory clinical response [20].

Osteoarticular blastomycosis is more difficult to treat and is more prone to relapse [19, 30]. Patients with osteoarticular blastomycosis should receive a minimum of 12 months of antifungal therapy [30]. Surgery reportedly plays a minor role in the treatment of osteoarticular blastomycosis [19], and there are no specific guides in this regard. Some patients can improve without surgical intervention; however, surgical procedures have been performed in most reports. Therefore, depending on the analysis of each individual case, surgery should be considered (i) for diagnosis through deep tissue sampling, (ii) as a co-adjuvant to antimicrobial therapy by means of draining abscesses or debridement of bone or soft tissues to facilitate the healing of affected areas [1], or (iii) to correct spinal deformities [31].

Prognosis

Osteoarticular blastomycosis requires prolong treatment because it is more difficult to treat and more likely to result in relapse [30]. The infection can spread by means of direct extension from an affected bone to soft tissues and nearby joints, with complications like abscesses and septic arthritis. The progressive destruction of bone can lead to pathological fractures [22]. In one series of 45 patients with blastomycosis of the bone or joints, residual symptoms were reported in 24% of patients; the most frequent symptoms were pain and limited range of joint mobility [1].

Conclusions and Future Directions

Although blastomycosis arthritis is an infrequent clinical manifestation of a relatively rare disease, cases have been reported from many countries around the world. The disease

occurs mainly in individuals who engage in outdoor activities or are exposed to decomposing plant material as well as in individuals with some form of immunosuppression. It is necessary to maintain a high index of clinical suspicion to perform appropriate microbiological testing, avoid delayed diagnoses and initiate timely antimicrobial treatment.

It is expected that advances in basic science techniques, such as sequencing the genome of the microorganism and the identification of as-yet-unknown virulence factors and critical factors for the transition to the yeast phase, will allow advances in molecular diagnostic methods and the development of new medicines with greater specificity and reduced toxicity [32]. Molecular techniques like real-time PCR could provide much more rapid diagnoses from the various available clinical specimens or even from fungal cultures themselves [33]. In spite of several promising reports, it is necessary to carry out additional clinical studies to define the clinical role of new azole agents, such as voriconazole, isavuconazole and posaconazole [34–36].

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Candida Arthritis

23

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Introduction

Candida was initially recognized as a human pathogen in 1940 in a case of endocarditis and has since emerged as the most common human fungal pathogen [1, 2]. Then, in 1967, the first case of native non-prosthetic *Candida* arthritis was published in the English literature [3]. Medical advances have fostered a rise of invasive candidiasis by increasing the number and length of survival of immunosuppressed patients [4]. In this group of patients with invasive candidiasis, a rise in morbidity and mortality, and emergence of resistant non-*albicans* species has been noted [5]. *Candida* arthritis is an uncommon entity and a form of invasive candidiasis in which gaps exist regarding the epidemiology, clinical manifestations, outcomes, and management [3]. The optimum treatment of *Candida* arthritis is being elucidated, but at this moment the standard of care involves a combination of surgical and medical management.

The purpose of this chapter is to provide an overview of the etiology/microbiology, epidemiology of *Candida* species, and to discuss the pathogenesis, clinical manifestation, diagnosis, and therapy of *Candida* arthritis.

Background: What Are *Candida?*

The name *Candida* comes from the Latin word *candidus* which means white. *Candida* species belong to the family of fungi. Fungi exist either as molds or yeasts. Molds replicate sexually or asexually and form multicellular filaments known as hyphae [6]. Yeasts are single-celled organisms that replicate asexually by budding or fission; budding cells can elongate in a filamentous appearance called pseudohyphae. *Candida* species are yeasts that reproduce by budding [7]. The ability to phenotypically switch from yeast to hyphae is considered an important pathogenic characteristic of many *Candida* species.

Candida species grow well on standard blood culture broth [8] and sheep blood agar medium and do not require special fungal media for isolation. On growth, *Candida* colonies depict characteristic morphologies, depending on the species, from smooth, glistening, cream like white (resembling staphylococcus colonies) to wrinkled, dry colonies [1, 4]. On Gram-staining, *Candida* organisms can be seen as round or oval Gram-positive. Hyphae and pseudohyphae can be observed with 10% potassium hydroxide [4, 7], and fluorescent uptake can be detected using calcofluor-white stain [1, 9] (Figs. 23.1, 23.2, and 23.3).

There are more than 200 species of *Candida*, and approximately 20 of them may be pathogenic to humans [10], *C. albicans* being the most common of them. *Candida* are usually grouped as *C. albicans* and non-*albicans Candida* species. Of the non-*albicans* group, *C. parapsilosis* and *C. glabrata* are most common; other important members are *C. tropicalis*, *C. lusitania*, *C. krusei*, *C. guillermondi*, and *C. auris*. It is important to identify *Candida* at the species level for diagnostic and therapeutic reasons. Various methods, beyond the scope of this chapter, can be used to identify *Candida* species ranging from biochemical metabolic tests to the use of matrix-assisted laser desorption/ionization time-of-flight-mass spectrometry (MALDI-TOF MS) [1, 11].

Candida Infection

Candida species are well adapted to the human host and frequently colonize skin and mucosae as commensal (maybe even beneficial) organisms. When the balance is disrupted, illness may ensue. For *Candida* species to cause

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_23

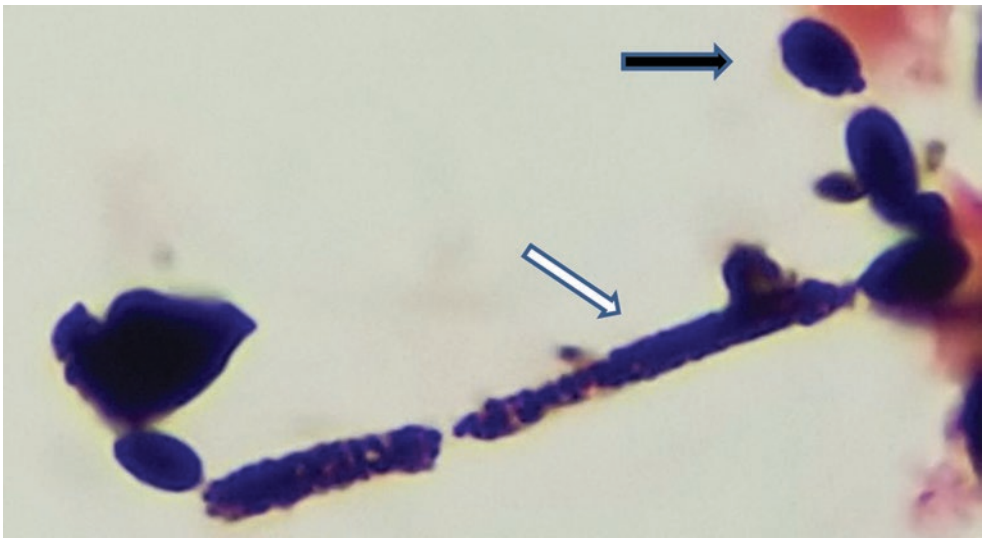

Fig. 23.1 Morphology of *Candida albicans* on Gram stain. Pseudohyphae *(white arrow)* and blastoconidia *(black arrow)* can be observed with candidiasis

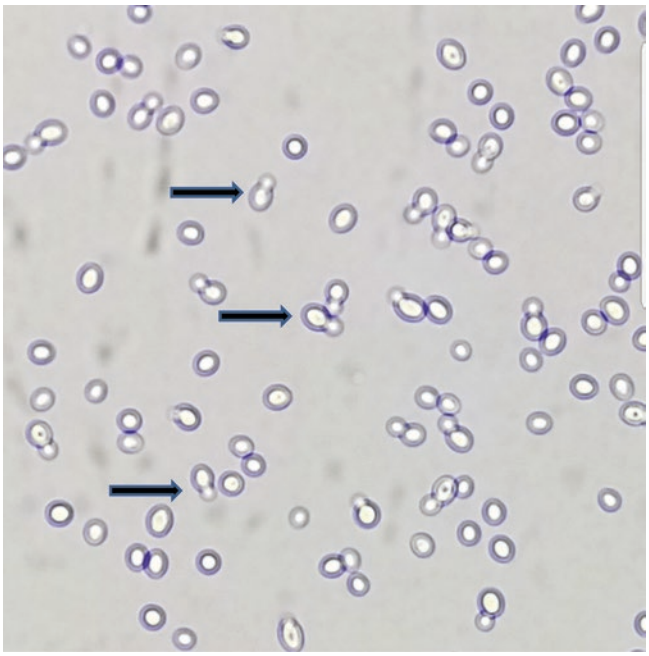

Fig. 23.2 Wet mount of *Candida albicans* demonstrating oval budding yeast 2–6 um in diameter *(black arrows)*

disease they must first colonize the individual and then become invasive. *Candida* can become invasive when they grow excessively and overwhelm the host, when natural barriers are disrupted, when the immune system fails to contain them, or when they are directly inoculated into sterile tissues.

Candida colonization is common; it is estimated that 25–50% of healthy individuals have *Candida* oral colonization at a given point in time, with *C. albicans* composing 70–80% of those isolates [6, 12]. Colonization increases in immunosuppressed hosts such as those with human immunodeficiency virus (HIV), diabetes, or patients on antineoplastic chemotherapy. Patients on broad-spectrum antibiotics and patients with metabolic conditions (e.g., diabetes, acidosis) have mucosal overgrowth of *Candida*. Medicines that diminish gastric acidity, such as proton pump inhibitors or Histamine-2 blockers, promote *Candida* gastrointestinal colonization (Table 23.1). Skin colonization is also common, especially around skin folds where hot and humid conditions dominate. Several immune disorders that affect T lymphocyte cytokine production have been associated to chronic mucocutaneous candidiasis [13]. With overgrowth at these colonized sites, if mucosal integrity or skin integrity is compromised, *Candida* dissemination to the bloodstream may occur. Artificial, invasive devices such as endotracheal tubes, intravascular catheters, indwelling bladder catheters, and others can become contaminated by *Candida* and from them disseminate and affect target organs [6, 12]. The most common mode of acquisition of *Candida* arthritis is through hematogenous spread, for example from contaminated central vascular catheter, a disrupted gastrointestinal mucosa with subsequent dissemination, direct intra-articular inoculation, or spread from a contiguous focus of infection [3]. Infrequently, but importantly, another mechanism is direct inoculation into the sterile joint space by surgical procedures such as prosthetic joint implantation or revisions, intra-articular injection of corticosteroids or other medications, and penetrating trauma to the joint space [14–17]. Finally, contiguous extension from adjacent osteomyelitis or soft tissue infections into the joint space has been described in bacterial arthritis [18].

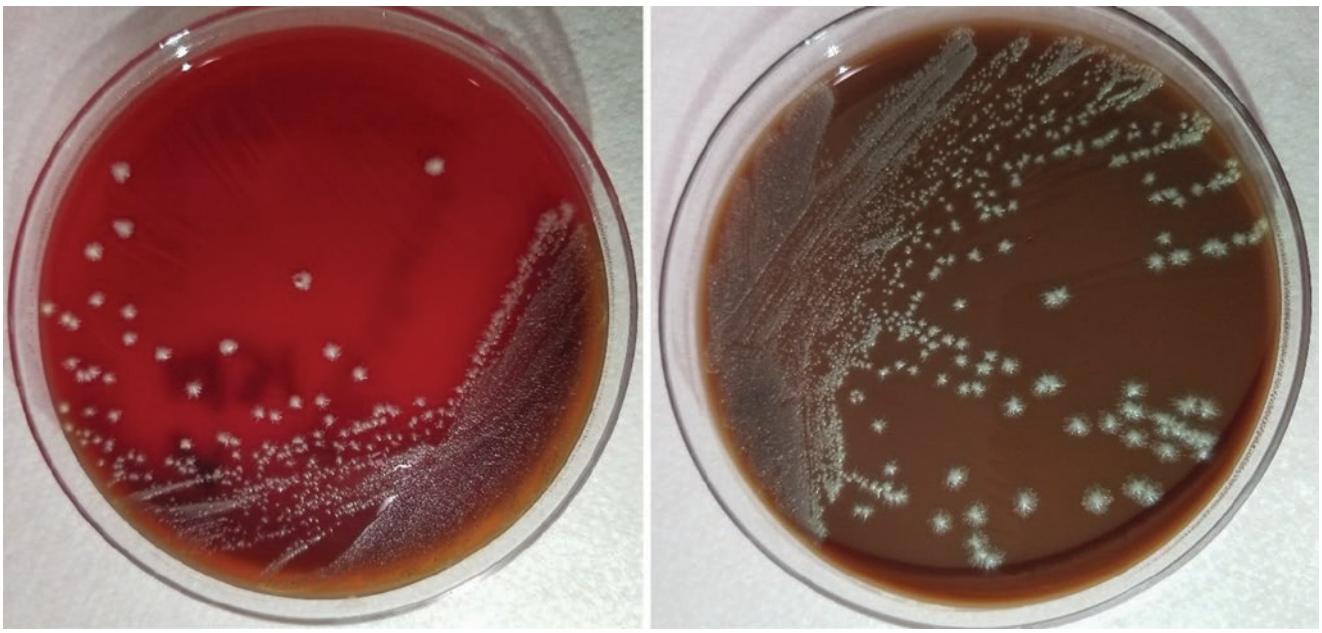

Fig. 23.3 Colonies at 48 hours, growing on standard 5% sheep blood agar *(left)*, and on chocolate agar *(right)*. The morphology of the colonies is reflective of *Candida albicans:* glistening, white-cream, exhibiting mycelial projections into the agar

Table 23.1 Patients at risk for *Candida* arthritis

Patient population	Risk factors	Prevention
Neonates	Prematurity Very low birth weight (<1500 grams) Indwelling catheters and foreign material Loss of skin integrity	*Infection prevention* Monitor *Candida*-related infections/colonization Prophylaxis: Fluconazole/nystatin Removal of central lines/endotracheal tubes Use of central line bundles Monitoring central line infections Frequent physical examination Evaluate mucocutaneous *candidiasis*
	Broad spectrum antibiotics[a] Medications decreasing gastrointestinal acidity[a] Hyperglycemic states (medication, diabetes, enteral feeding, sepsis)[a] (All promote mucocutaneous, skin, and gastrointestinal colonization with *Candida*)	*Antimicrobial/medication/feeding stewardship*[b] Proper utilization of the following: Empiric antimicrobials Duration of therapy Proton pump inhibitors/H_2 blockers Dexamethasone/parenteral feeds
Immunosuppressed Primary immune deficiency states	Prolonged neutropenia Chemotherapeutic induced Solid organ transplants recipients	*Infection prevention (As above) + additional bacterial prophylaxis to prevent invasive opportunistic infections*
Secondary immune deficiency states	Malnutrition Chronic illness Hemodialysis Rheumatoid arthritis Immunomodulatory therapies[a]	Levofloxacin, trimethoprim/sulfamethoxazole *Antimicrobial/medication/feeding stewardship* [b]
Immunocompetent	Loss of skin integrity Burns, chronic wounds, trauma Trauma: introduction or dissemination of *Candida* Surgical procedures (gastrointestinal/thoracic) Intra-articular steroid injections/intravenous drug[a]	Proper wound care, source control *Antimicrobial/medication/feeding stewardship* [b]

[a]Risk factors apply to neonates, immunosuppressed, and immunocompetent
[b]Prevention applies to neonates, immunosuppressed, and immunocompetent

Virulence Factors

Candida species can express different factors that determine their phenotypic behavior and ability to cause disease, such as attachment properties, biofilm formation, morphology switching, and hydrolytic enzymes secretion [4]. Extracellular hydrolytic enzymes mediate virulence by disrupting the host's mucosal membranes and degrading proteins involved in the immunologic cascade. A notable family of extracellular hydrolytic enzymes is aspartic proteases (Saps) seen in *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. lusitaniae* [19]. Adhesion proteins, particularly seen in *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*, facilitate attachment to host tissues and foreign materials, allowing these strains to be more virulent [4, 20, 21]. The genes for these adhesion proteins are upregulated by hyperglycemic states leading to impairment of the complement cascade to opsonize fungi. The epithelial adhesin (PEA), seen in *C. glabrata*, attaches to host's tissues or prosthetic material, and promotes cell division and proliferation, and biofilm formation [21]. Biofilm formation is recognized as an important step in virulence. *Candida* species that produce biofilms upregulate genes that encode for efflux pumps, and the biofilms themselves form a protected niche that impairs penetration of antifungals [21–23], both factors that lead to treatment failure. Species known to produce biofilm include *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *and C. glabrata*. Once an isolate attaches to the affected tissue, phenotype switching from the yeast to hyphal phase allows *Candida* to colonize, survive, and invade human tissues [7, 24]. *C. albicans* is the most efficient and virulent of the *Candida* species as it is associated with the highest rate of end-organ damage and higher attributable mortality [25, 26], followed by *C. tropicalis* [27]. Both *C. albicans* and *C. tropicalis* are also the two most common *Candida* causing septic arthritis [3, 28, 29]. *C. glabrata* is commonly implicated in candidemia, but rarely in *Candida* arthritis, suggesting it does not have the inherent virulence factors to infect the synovial fluid [3].

Host Immune Response

Recent research has highlighted the pathogenesis of *Candida* infections with a focus on the host's mechanisms of defense, alterations in the innate and adaptive immunity, and genetic susceptibility to invasive infections [30–33]. Once *Candida* initiates systemic infection, the immediate host response is through the innate immune system. Neutrophils, monocytes, and macrophages are part of the innate immune response to *Candida* and immunosuppressive agents or conditions promoting neutropenia or alterations in neutrophil function increase the probability of invasive candidiasis [4]. Adaptive immune response follows, mainly cellular, with prominent role by $CD4^+$ T_H17 cells. Their role is illustrated by mutations in STAT3 transcription that result in decrease of function and lead to mucosal invasion by *C. albicans* as seen in Hyperimmunoglobulin E syndrome or Autoimmune Polyendocrinopathy with Candidiasis and Ectodermal Dystrophy [4, 34–42]. Humoral immune response, while present and strong, does not seem to have a protective role, even though it may mediate some cellular functions [24, 43].

Epidemiology of Candida Infection

In the United States candidemia is overall the fourth most common cause of nosocomial blood stream infection, and third most common among premature neonates [36, 44–49]; annual costs are estimated at $2 billion dollars, with a mortality of over 40% [50]. Over a 5 year period (2000–2005), the incidence of candidemia-related hospitalization per 100,000 population increased by 52%, from 3.65 to 5.56 patients in the United States, and the incidence among hospitalized patients increased by 49% from 0.28 to 0.42 cases per 1000 hospitalizations [51].

Certain groups (see Table 23.1) are predisposed to disseminated candidiasis, such as neonates (especially those born prematurely), hosts that are immunosuppressed, factors that disturb skin integrity (burns, chronic wounds), presence of foreign material (prosthetic material, endotracheal tubes, intravenous catheters), hyperglycemic states (diabetes, total parenteral nutrition, chronic steroid use), factors that alter the gastrointestinal flora (H2 blockers, proton pump inhibitors), and use of prolonged broad spectrum antibiotics. A study in a pediatric intensive care unit found an incidence of candidemia of 3.5 per 1000 admissions; the presence of a central vascular catheter, oncologic pathology, receipt of an antibiotic against anaerobes for more than 3 days, and vancomycin administration were all independent risk factors [52, 53].

Of the *Candida* species, *C. albicans* is the one most commonly associated with infections in humans. Nonetheless, more recently there has been a shift to the non-*albicans* *Candida* species, now accounting for more than half of invasive infections [7, 35, 50, 54–58]. In a retrospective study from 1992 to 2000 among pediatric oncology patients, *C. albicans* accounted for only 29% of the cases [27]. One notable non-*albicans* *Candida* species is *C. parapsilosis*, which has increased in prevalence over the past two decades, constituting the second most common cause of systemic candidiasis in a cohort of neonates weighing less than 1000 grams at birth [26, 59, 60]. Other species that are known pathogens to humans and have resistant antifungal susceptibilities include *C. lusitaniae*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guillermondii*, *and C. dubliniensis* [7].

Data is scant on the epidemiology and frequency of *Candida* arthritis. It is unclear what proportion of patients with candidemia will develop *Candida* arthritis. Nonetheless, *Candida* arthritis seems to be increasing in incidence in immunosuppressed populations such as neonates, hosts with advanced HIV infection, primary immune deficiency states (e.g., chronic granulomatous disease or myeloperoxidase deficiency), or secondary immunosuppressed states (due to immunomodulatory, and chemotherapeutic therapies) (see Table 23.1) [7]. In general, *Candida* arthritis is most commonly acquired through hematogenous spread. In a 47-year retrospective review of the English literature for native non-prosthetic *Candida* arthritis, 112 published cases were found; the mode of acquisition was hematogenous in 81% and direct inoculation in 19%; 32% of patients had preexisting candidemia, and 11% had candidemia at the time of diagnosis. The median age was 40 years (ranging from less than one month to 84 years), and 36% of cases were in the pediatric population including 10% in neonates. Of interest, 95% of the pediatric patients had infection following hematogenous dissemination in comparison to 74% of adults ($P = 0.005$). The most common underlying conditions were surgery (35%), hematologic malignancies (16%), solid organ transplant, trauma, and intravenous drug use (9%, each), and solid organ tumors (4%). *C. albicans* was identified in 63% of cases. The non-*albicans Candida* species isolated were *C. tropicalis* (14%), *C. parapsilosis* (11%), *C. krusei* (4%), and *C. glabrata*, *C. lusitaniae*, and *C. guilliermondii* (2%, each) [3]. In cases not acquired through disseminated candidiasis, the non-*albicans Candida* species have been most commonly isolated [1]. Of note, up to 85% of *Candida* arthritis in infants occurs in children younger than 6 months of age [61]. The postulated pathogenesis for a predilection in this young age group is delay in closure of the epiphyseal plate, allowing hematogenous spread to reach the joint space through the articular cartilage or through the bone cortex of the joint capsule [3].

Clinical Presentation

Candida infections can have a spectrum of manifestations ranging from mucocutaneous candidiasis to hematogenous dissemination to deep tissues and target organ involvement (such as the liver, abdominal viscera, spleen, eyes, heart, musculoskeletal, and brain). Depending on the age, immunosuppressed state of the host, and associated risk factors, *Candida* infection needs to be promptly considered as it is associated with high morbidity and mortality. For example, in neutropenic hosts, a potential fungal infection should be suspected, and empiric treatment initiated after 4 days of continuous fever non-responsive to broad-spectrum antibiotics. Concern for candidemia also arises in a host with clinical decompensation of unclear source and associated persistent thrombocytopenia. Other clinical findings that may lead to suspect *Candida* infection include hepatomegaly with elevated liver enzymes, especially if lesions are seen in the spleen and liver. Most cases of *Candida* arthritis arise in patients with known invasive candidiasis or as part of the initial candidemia presentation; therefore, a thorough musculoskeletal exam is needed in all cases of proven or suspected candidemia (Table 23.2) [3].

The clinical presentation of *Candida* arthritis in both children and adults is nonspecific and manifested by the common findings of pain, edema, erythema, limitation of movement, fever, and drainage of pus [3]. It can manifest acutely or in an indolent fashion; it can present as mono arthritis when caused by direct intra-articular inoculation, or as mono or polyarthritis when secondary to hematogenous spread [62]. Two-thirds of cases of *Candida* arthritis are acute, presenting

Table 23.2 Diagnostic evaluation of suspected or proven candidiasis/candidemia/arthritis

Physical examination evaluating from mucocutaneous candidiasis to hematogenous dissemination *Ophthalmology evaluation:* Retinal hemorrhages, Roth spots, endophthalmitis, chorioretinitis *Skin:* Evaluate for lesions/trauma and embolic findings (Janeway lesions, Osler nodes) *Spleen, Liver:* Hepatosplenomegaly (hepatosplenic candidiasis) *Renal:* Hydronephrosis, tenderness to costovertebral palpation *Cardiac:* Murmurs (especially in hosts with damaged heart valves or prosthetic material) *Neurology:* Cranial nerve deficits, or focal neurologic findings *Musculoskeletal:* Joint edema, heat erythema, limitation of movement	
General laboratory evaluation: Serum: CBC, CMP, ESR, CRP, blood cultures[a, b, c, d] (regular ± fungal), (1,3)-β-D-glucan, real time polymerase chain reaction, urine analysis/urine culture *Synovial fluid analysis:* Cell count, biochemistry, Gram/AFB stain, bacterial/fungal/mycobacterial cultures.	*Radiological evaluation:* (Dependent on physical/clinical findings) Head US, abdominal/renal US or CT, brain MRI w/wo contrast, chest radiograph, echocardiogram *Concern for septic arthritis:* Ultrasound, computed tomography, and/or MRI if concern for superimposed osteomyelitis

Abbreviations: *AFB* acid fast bacilli, *CBC* complete blood cell count, *CMP* complete metabolic panel, *CRP* C-reactive protein, *CT* computed tomography, *ESR* erythrocyte sedimentation rate, *MRI w/wo* magnetic reasoning imaging with and without, *US* ultrasound

[a]If concern for endocarditis three sets of blood cultures, separate venipunctures (at least 1-hour gap from first to last)

[b]Two to four blood cultures should be obtained with volume of 20–30 mL of blood per culture in adults and injected into at least two aerobic vials or broth medium

[c]In infants and children two or more blood cultures are also needed; the volume to be collected is dependent on the weight in kilograms (2 mL for weight ≤ 2 kg; 4 mL for 2.1 to 12.7 kg and 10 mL for 12.8 to 36.3 kg) [8]

[d]If a positive culture is obtained, follow-up cultures should be collected every 1–2 days until clearance is documented [52]

as suppurative synovitis; however, chronic mono-articular *Candida* arthritis has been reported in immunosuppressed subjects [1]. Occasionally, osteomyelitis and septic arthritis due to C*andida* can be seen days to weeks, and even months to years, after resolution of candidemia [4, 63]. In the acute presentation, symptoms are constitutional in nature, such as fever, and are accompanied by synovial symptoms of tenderness or restriction in movement of the affected joint [4, 23, 62, 64]. Indolent presentations are accompanied by mild, nonspecific symptoms, and the diagnosis may be delayed months to years [62]. Polyarthritis is more commonly seen in neonates, and mono arthritis in older populations. The most common affected sites are the knee (75%), hip (15%), shoulder (7%), ankle (5%), carpal (3%), elbow (4%), tarsal (2%), wrist (2%), and costochondral (1%) [32].

Subjects that use intravenous drugs can present with *Candida* arthritis that affects the fibrocartilaginous joints, including the costochondral, sacroiliac joints, and the intervertebral disks [65]. Insidious presentations can be seen in cases of intra-articular inoculation by injection or surgical procedures. The presentation is often mono-articular with lack of fever, constitutional symptoms, and associated joint pain and stiffness [62, 66]. In prosthetic joint infections, the clinical symptoms often mimic those of prosthetic mechanical failure, frequently delaying the diagnosis [62].

Diagnostic Evaluation of Candida Infection

Clinical Suspicion

The clinical characteristics of *Candida* infection are discussed above and will not be repeated here, except to emphasize the nonspecific presentation and the need to have a low threshold for suspicion, particularly in patients with risk factors for *Candida* infection and compatible clinical presentation. In the populations at risk, a single positive culture for *Candida* warrants a thorough evaluation and physical examination for end organ compromise (see Table 23.2). In the neonate (especially the extremely premature), this should include ophthalmologic examination, ultrasound of the head, abdomen and renal system, lumbar puncture for cerebrospinal fluid analysis, catheterized urine analysis with culture, and an echocardiogram for potential endocarditis (see Table 23.2). Due to predilection for endocarditis, a cardiac examination is needed in evaluating for murmurs and a thorough exam looking for potential metastatic emboli, especially in hosts with a damaged heart valve or prosthetic material. It has been described that metastatic lesions and embolic events are more common in endocarditis caused by *Candida* in comparison to bacterial etiologies [6]. It is important to obtain at least three sets of blood cultures from separate venipuncture sites, with at least 1-hour gap from the first to last, followed by an echocardiogram. Since the eye is a common site of seeding in hematogenous candidiasis, an ophthalmology evaluation is encouraged within 1 week from initial presentation. Hematogenous seeding of the renal system can result in cystitis, pyelonephritis, pyonephrits, acute lobar nephronia, or perinephric abscess formation. A urine analysis, urine culture, and ultrasound in suspected renal involvement should be obtained.

Routine Blood Tests

Initial evaluation should include routine blood tests such as complete blood count (CBC), complete metabolic panel (CMP), blood cultures, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) (see Table 23.2). In 112 patients with *Candida* arthritis, the median (range) serum white blood cell count was 10,750 cells/mm^3 (160–36,500 cells/mm^3), neutrophils 45% (10% to 90%), ESR 62 mm/hr (10–141 mm/hr), and CRP 2.6 mg/L (0.05–9.5 mg/L) [3]. Compared to pyogenic arthritis, *Candida* arthritis causes less systemic inflammation, but there is much overlap between these two entities, making differentiation difficult on these parameters alone.

The current gold standard for candidemia is isolation of *Candida* in a blood culture. Blood cultures have a specificity of 100% since growth of *Candida* from a sterile site is never regarded a contaminant. Unfortunately, sensitivity is low and blood cultures are positive in less than 50% of patients with autopsy-proven invasive candidiasis [8, 67, 68]. To increase the chances of isolating *Candida*, two to four blood cultures should be obtained with volume of 20–30 mL of blood per culture in adults and injected into at least two aerobic vials or broth medium; lysis-centrifugation may be used to increase the yield. In infants and children two or more blood cultures are also needed; the volume to be collected is dependent on the weight in kilograms of the patient, though (2 mL for weight $\leq$ 2 kg; 4 mL for 2.1–12.7 kg and 10 mL for 12.8–36.3 kg) [8]. Many authors opine that routine bacterial and fungal cultures have similar sensitivities for candidemia, and hence fungal cultures offer no advantage over routine bacterial cultures. Still, some authors believe that mycological media, at least in theory, can provide an advantage in isolating *Candida* due to the addition of nutrients, antibiotics to suppress competitive bacterial growth, and utilization of a lysing agent to release viable phagocytes [4]. The use of an automated blood system is advocated as it allows for a quicker detection of candidemia and bacteremia. If a positive culture is obtained, follow-up cultures should be collected every 1–2 days until clearance is documented [52].

Fungal Markers

The low yield of blood cultures has spurred the use of tests that identify *Candida* antigens or DNA, with mixed results. One such test is the detection in the serum of (1,3)-β-D-glucan (BDG). BDG is a cell wall component found in many fungal species of *Candida*, *Aspergillus*, *Fusarium*, *Histoplasma*, *Pneumocystis jirovecii*, and many other fungi. Since invasive candidiasis has a low prevalence, the BDG test may generate false positive results, so results should be interpreted with caution and should be used as supportive criteria only [69]. False-positive results can occur in patients with recent administration of intravenous immunoglobulin, albumin, hemodialysis (due to cellulose in the hemodialysis membranes), transfusion with fresh frozen plasma or packed red blood cells, bacteremia, fungal colonization, use of surgical gauze, enteral nutrition, hosts with mucositis or gastrointestinal mucosal breakdown, and intravenous antibiotic administration specially with piperacillin/tazobactam [52, 67, 70, 71]. False negative results occur in patients receiving antifungals, and patients with hyperbilirubinemia and high triglyceride levels. BDG performance improves when found positive in two consecutive results [67, 72]. In an adult population with oncologic disease and 10% prevalence of invasive fungal infection, a meta-analysis on the performance of two sets of BDG found a sensitivity of 49.6%, specificity of 98.9%, positive predictive value (PPV) of 83.5%, and negative predictive value (NPV) of 94.6%, for the detection of invasive fungal disease [72, 73]. The low sensitivity highlights the importance of correlating BDG results with clinical, microbiological, and radiological findings; while the high NPV supports the use of BDG in ruling out invasive candidiasis. Recent studies have suggested utility of BDG as a prognostic marker of treatment response, showing that a decrease in BDG levels while on antifungal therapy is associated with a successful treatment (PPV = 90%), and an increase in BDG correlates with treatment failure (NPV = 90%) [74]. Studies also suggest that BDG monitoring in patients at risk of invasive candidiasis can identify cases of invasive candidiasis days to weeks prior to positive blood cultures; thus, shortening the time of initiation of antifungals and decreasing associated morbidity and mortality [75, 76].

New diagnostic modalities utilizing DNA amplification techniques via real-time polymerase chain reaction (RT-PCR), or similar, have increased the sensitivity to detect *Candida* organisms without decreasing specificity [4, 77]. *Candida* PCR is currently available for whole blood and blood fractions, but it has not been validated for invasive candidiasis in multicenter studies [67]. For invasive candidiasis, PCR from plasma or sera is more sensitive than whole blood. Comparing PCR to serum BDG in invasive candidiasis, PCR seems more sensitive (80% vs 56%; *P* value: 0.03), but both have comparable specificity of around 70%. In the evaluation of invasive candidiasis, when blood cultures are combined with BDG, the sensitivity rises from less than 50% for blood cultures alone, to 79% for blood cultures combined with BDG testing, and to 98% for blood cultures combined with PCR [68].

Joint Aspirate

Evaluation of arthritis ultimately requires evaluation of the joint. Clinical suspicion of any form of septic arthritis, including *Candida* arthritis, should lead to radiographic evaluation with ultrasound, arthrocentesis of the affected joint or surgical drainage if the hip or shoulder is involved (especially in children). Magnetic resonance images of the affected joint should be considered if there is concern for adjacent osteomyelitis.

Aspirated synovial fluid should be obtained in a heparinized syringe to prevent clot formation and optimize the enumeration of leukocytes. The fluid should be evaluated for Gram-stain, aerobic and anaerobic bacterial cultures, fungal cultures, staining and culture for mycobacteria, and cell count with differential and histopathological evaluation. The WBC count has a median, (range) value of 27,500 cells/mm^3 (100–220,000 cells/mm^3) with neutrophils 90% (24–98%), glucose 59.5 mg/dL (2–119 mg/dL), and protein 5.15 g/dL (2.8–6.5 g/dL) [25]. In both pyogenic arthritis and *Candida* arthritis, the glucose and protein values have low sensitivity and specificity and are unreliable [14, 78]. Histopathology findings of the synovium can show nonspecific mononuclear inflammatory reaction, thickening of the synovium, and lack of granuloma formation (which may help distinguish *Candida* arthritis from other fungal arthritides) [4, 61]. The synovial fluid Gram-stain will be positive in only approximately 9% of samples (in comparison to 50% in cases of pyogenic arthritis) [14, 78], making it of limited diagnostic value. For that reason, Gram-stain must be evaluated with caution as false positive results can occur from artifacts in staining due to increased cellular debris and/or presence of mucin. The rate of successfully isolating *Candida* from synovial fluid from proven cases of *Candida* arthritis is not known but is thought to be low. Therefore, if a patient has candidemia and clinical or radiologic findings suggestive of septic arthritis, even if no growth in synovial cultures, a presumptive diagnose can be made, and the patient should be treated accordingly. BDG has not been validated from synovial fluid, and its use is discouraged. Similarly, PCR has not been validated in multicenter trials for invasive candidiasis and may be negatively affected by many technical problems and inhibitors in complex synovial fluid, so it should not be used outside of research situations; therefore, the use of PCR testing for samples other than blood is not routinely endorsed [52, 67].

Treatment of *Candida* Arthritis

The goal of therapy is to start empiric antifungals as soon as candidemia or invasive candidiasis is suspected, remove contaminated central venous catheters, and drain infected material for timely source control [75, 79–82] (Tables 23.3 and 23.4).

Surgical Treatment

The Clinical Practice Guideline for the Management of Candidiasis (2016 update) by the Infectious Diseases Society of America [52] recommends joint drainage in all cases of septic arthritis, both for therapeutic and diagnostic reasons (see Table 23.3). The goals are to relieve pressure to the joint, isolate an organism to obtain a susceptibility profile, tailor antifungals accordingly, and ultimately preserve joint function [83]. In cases of *Candida* arthritis involving a prosthetic device, it is strongly recommended to remove the prosthesis [52]. If the prosthesis cannot be removed, the patient will require chronic antifungal suppression [18]. Surgical options for drainage include arthroscopy and open arthrotomy. These surgical procedures allow for direct visualization of the affected joint to irrigate, lyse adhesions, and remove purulent material [83–85]. In septic arthritis of the hip, open surgical drainage should be performed immediately, ideally within 6–12 hours from clinical presentation as it constitutes a medical emergency [14, 86–94]. In joints other than the hip, single or multiple needle aspirations can be initially done in lieu of surgical drainage; however, surgical drainage is recommended when multiple needle aspirations fail to control the infectious process [87, 90–95]. Needle aspiration may be considered if the joint is accessible, has high probability of adequate drainage, and the patient lacks poor prognostic factors such as neurovascular compromise, sepsis, prolonged duration of symptoms prior to evaluation, and significant comorbidities [90, 91, 93]. In children, well-established situations recognized in need of surgical drainage include involvement of the hip joint (some authors also consider the shoulder as it often has delayed presentation and complicated disease course); large amounts of pus, debris, fibrin, or loculation within the joint space; and lack of clinical improvement within 3 days of appropriate antimicrobial therapy [14, 86, 95–99].

Table 23.3 Surgical treatment of candidiasis/candidemia/*Candida* arthritis

Procedure	Purpose	Comment
Surgical drainage via arthrocentesis vs arthrotomy	*Diagnostic:* synovial collection for diagnosis (culture/biochemistry) *Therapeutic:* Relieve pressure on the joint	*Surgical drainage:* Hip and shoulder to relieve pressure within 6–12 hours (medical emergency) Allows: Direct visualization, irrigation, lyse adhesion
Single or multiple needle aspirations	*Diagnostic:* (culture/biochemistry) *Therapeutic:* Relieve pressure on the joint	Not indicated for hip and shoulder joint Surgical drainage indicated when multiple needle aspirations fail to obtain source control
Removal of prosthesis or central line	Remove nidus of infection (source control)	If prosthesis cannot be removed: need chronic antifungal suppression.

Table 23.4 Empiric antifungal therapy for confirmed/suspected *Candida albicans,* non-*albicans Candida* pending final susceptibilities

Clinical scenario	Antifungal therapy[a, b, c]
Empiric antifungal therapy for suspected invasive *Candida* infection	Echinocandin, amphotericin, fluconazole[d]
Confirmed *Candida albicans*	Fluconazole
Confirmed non-*albicans Candida*	Echinocandins or amphotericin

[a]Broadly in order of preference
[b]Confirm susceptibilities to narrow antifungal therapy accordingly: According to susceptibilities consider fluconazole, voriconazole, micafungin, or amphotericin B deoxycholate and liposomal amphotericin B
[c]Fluconazole and amphotericin B deoxycholate are the only antifungals with reliable central nervous system, ocular or renal penetration (where the echinocandins have poor or unknown penetration)
[d]If the patient is stable and no prior exposure to fluconazole

Antifungal Therapy

Besides source control, prompt initiation of empiric antifungals is imperative since delay is associated with increased morbidity and mortality (see Tables 23.4 and 23.5) [75,

Table 23.5 Duration of treatment of candidiasis

Duration of therapy[a]: General 2–6 weeks	
Oropharyngeal candidiasis	2 weeks
Esophageal candidiasis	3 weeks
Candidemia without metastasis	2 weeks from clearance + clinical improvement
Invasive candidiasis	2 weeks from clearance + clinical improvement
Intravascular infections	
Native valve endocarditis	6 weeks (minimum after valve replacement)
Prosthetic valve endocarditis	6 weeks minimum + chronic suppressive therapy
Chorioretinitis without vitritis	4–6 weeks or longer with ongoing lesions
Central nervous system Candidiasis	6 weeks minimum (determined by CSF evaluation, radiologic resolution, and clinical improvement)
Candida osteoarticular infections	
Osteomyelitis Arthritis	6 months–12 months 6 weeks (remove prosthetic device, if device cannot be removed the patient will need chronic suppression with fluconazole if isolate shows a susceptible profile)

Adapted from 2016 Update by the Infectious Diseases Society of America [52]
[a]In general duration of therapy is determined by source control and clinical response

79–82]. Choice of the best empiric antifungal regimen is based on suspicion of *Candida* infection., final identification of the *Candida* species, site of infection, and stratification of risk factors (such as immunosuppressive state), and prior exposure to antifungal agents. Empiric treatment should be initiated whenever there is a strong suspicion of *Candida* infection such as in a patient with risk factors and compatible clinical presentation or when "yeast" are visualized in Gram-stain or culture. Once "*Candida*" is identified it is important to determine the species to better target treatment, since some species may be more resistant than others. Finally, isolates should be tested for susceptibility to antifungals (which may take few days to result) to decide on definitive treatment. Infectious Diseases specialists should be consulted to guide on optimal drug therapy, monitoring of medication levels, diagnostic evaluation, and duration of therapy. There are generally three options for antifungal treatment of invasive *Candida* infection: (i) the triazoles (all either intravenous or oral) which include mainly fluconazole, but also voriconazole, posaconazole, and isavuconazole; (ii) the echinocandins (intravenous only) which include caspofungin, anidulafungin, and micafungin; and (iii) polyenes (intravenous only) that include amphotericin B deoxycholate, and lipid formulations of amphotericin B (which have less nephrotoxicity than deoxycholate) (see Table 23.6 for dosing guidelines). A fourth group which is rarely, if ever, used for osteoarticular infection is the pyrimidine group (oral only), with the only approved agent flucytosine (5-fluorocytosine), which can have significant toxicity of the bone marrow, should be avoided in renal dysfunction, and should never be used as a single agent due to rapid development of resistance (it is used in combination with amphotericin B or fluconazole). *Candida* species that have resistance to fluconazole include *C. glabrata* in about 50% of cases, 100% of cases in *C. krusei* [100]. Although the prevalence of fluconazole resistance to *C. tropicalis* is low, resistance has been increasing in hosts with prior exposure to this drug [21, 101, 102]. In general, voriconazole offers a broader spectrum of activity in comparison to fluconazole for *C. glabrata* and *C. krusei*; however, resistance is also documented. (Interestingly, fluconazole is more active against *C. tropicalis* in comparison to voriconazole [101].) The echinocandins are fungicidal and offer good empiric coverage; however, resistance

Table 23.6 Antifungal formulations, indications, and dosing

Generic name	Usual daily dose	Max single dose	Comments
Triazoles			
Fluconazole PO and IV[a] *Tablets:* 100 mg, 150 mg *Suspension:* 10 mg/mL, 40 mg/mL	Cystitis/Oropharyngeal: 3 mg/kg/dose every 24 hours	400 mg	IV to PO is 1:1 conversion CNS penetration, only triazole with excellent urine penetration *C. krusei* intrinsically resistant
	Esophagitis: 6 mg/kg/dose every 24 hours		
	Candida prophylaxis: 6 mg/kg/dose every 24 hours		
	Invasive candidiasis: 12 mg/kg/dose every 24 hours	800 mg	
Voriconazole PO and IV[a] *Tablets:* 50 mg, 200 mg *Suspension:* 40 mg/mL	Pediatrics <2 years old: Undetermined	400 mg	Children require higher doses than adults Excellent CNS penetration IV to PO is 1:1 conversion **Through level 5–7 days into therapy (steady state)** **Goal: Prophylaxis: ≥0.5** **Treatment: ≥1** **Toxicity: ≥6**
	Children 2–12 years old or 12–14 and <50 kg: Intravenous: 9 mg/kg/dose every 12 hours for 2 doses followed by 8 mg/kg/dose every 12 hours		
	Children 2–12 years old or 12–14 and <50 kg: Oral: 9 mg/kg/dose every 12 hours		
	Children ≥15 years old or 12–14 and ≥50 kg: 6 mg/kg/dose q12h for 2 doses followed by 4 mg/kg/dose every 12 hours		
Echinocandins			
Micafungin IV[a]	Candida prophylaxis: 1 mg/kg/dose every 24 hours	50 mg	Infants <4 months require higher mg/kg/dose (consider ID consult) Poor CNS, ocular, and urine distribution
	IFI[a] Treatment: 3 mg/kg/dose every 24 hours	150 mg	
	Candida esophagitis: 4 mg/kg/dose every 24 hours		
	Aspergillus: 4 mg/kg/dose every 24 hours		
Polyenes			
Amphotericin B Deoxycholate IV[b]	IFI[a] Treatment: 1 mg/kg/dose every 24 hours	Undetermined	Deoxycholate preferred for urinary infections; Liposomal preferred for CNS infections Monitor electrolytes Pre- and post-hydration with normal saline recommended to reduce risk of AKI
	Esophagitis/Cystitis: 0.5 mg/kg/dose every 24 hours		
Amphotericin B Liposomal IV[b]	IFI[a] Prophylaxis: 1 mg/kg/dose every 48 hours OR 2.5 mg/kg/dose twice weekly		
	IFI[a] Treatment: 3–5 mg/kg/dose every 24 hours		

Data from references [52, 107–117]

Abbreviations: *AKI* acute kidney injury, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CNS* central nervous system, *h* hour, *ID* infectious diseases, *IFI* invasive fungal infection, *IV* intravenous, *kg* kilogram, *mg* milligram, *mL* milliliter, *PO* per os (oral)

[a]Drug monitoring: Triazoles, echinocandins: ALT, AST, and bilirubin at baseline and every 1–2 weeks thereafter

[b]Amphotericin B (lipid or deoxycholate): baseline serum creatine, magnesium, phosphate than daily in hospitalized patients, then twice weekly for outpatients

has been observed in *C. glabrata*, *C. guilliermondii*, and *C. parapsilosis.* Regarding amphotericin B, most clinically relevant *Candida* species are susceptible to this drug except for *C. lusitaniae*, and increasing resistance is being observed with *C. glabrata* and *C. krusei*.

Currently, there is no proven therapeutic superiority of one of the mentioned antifungals over the others. Nonetheless, it is accepted by most that the echinocandins should be considered the initial drugs of choice for suspected or proven candidiasis. This is based on their favorable safety profile, broad anti-*Candida* activity, and evidence of successful outcomes from individual and combined analyses (see Table 23.4) [52, 75, 103]. Amphotericin B has a broader antifungal spectrum than the echinocandins (mainly for other fungi besides *Candida*) but also has more toxicity (mainly renal). Still, it may be preferred over the echinocandins in certain situations; for example, in cases of severe disease, highly immune suppressed hosts, prior exposure to antifungals (e.g., for prophylaxis), or in cases of central nervous system, ocular or renal involvement (where the echinocandins have poor or unknown penetration). The triazoles (mainly fluconazole) are usually well tolerated but are less preferred for empiric treatment due to its relatively narrow spectrum. If *Candida* is subsequently identified as *C. albicans* (probably the most common scenario), fluconazole can then be substituted for the remaining of the treatment (and the echinocandin or amphotericin B stopped) for ease of administration and since *C. albicans* is almost universally susceptible to fluconazole. For the other non-*albicans Candida*, even though many are susceptible to fluconazole, due to increasing resistant pattern, it is advised to wait until susceptibility results are made available. Once susceptibility of the isolate to antifungals is reported, decisions for definitive therapy can be based on those results. Besides the obvious susceptibility, criteria may include considerations such as ease of administration (i.e., oral better than intravenous), tolerability, drug interactions, cost, availability, and others.

As expected, this general approach has many alternative scenarios. For example, the immunosuppressive state of the host must be considered. Patients with oncologic diagnosis and neutropenia have increased propensity of dissemination with *C. tropicalis*, which are increasingly resistant to fluconazole due to previous drug exposure [102]. Other considerations are prior exposure to fluconazole, recent surgical procedures, and age older than 2 years (variables found to be independently associated with candidemia by fluconazole resistant strains of *C. glabrata* and *C. krusei*) [104]. In the neonatal population, *C. albicans* and *C. parapsilosis* are the two species most frequently isolated from sterile sites, and these are usually susceptible to fluconazole; and other less frequently isolated species such as *C. tropicalis, C. lusitaniae*, and *C. guillermondii* are also usually susceptible to fluconazole in drug-naïve patients [100].

Follow-up blood cultures need to be performed every 1–2 days until clearance [52]. Duration of therapy for uncomplicated candidemia without secondary sites of infection is for two weeks from first negative blood culture and clinical improvement (see Table 23.5) [52]. Any central venous catheter associated with *Candida* blood stream infection should be removed immediately as prompt removal is associated with improved outcome, lower mortality, reduced duration of infection, and lower chances of end-organ dissemination [26]. For empirical treatment of suspected catheter-related candidemia, the use of an echinocandin or amphotericin B is generally recommended; in patients clinically stable, without triazole exposure in the previous 3 months and in setting with low risk of *C. krusei* or *C. glabrata*, fluconazole can be attempted [105]. Antifungal therapy of uncomplicated central line associated infections (bloodstream infection and fever resolving within 72 hours with no intravascular hardware and no evidence of endocarditis or thrombophlebitis) treatment is recommended for 14 days from removal of the catheter or from the first negative blood culture after removal of the catheter [105].

Antimicrobial Therapy for Candida Arthritis

Like above, empiric therapy for *Candida arthritis* is an echinocandin; lipid formulation amphotericin B is favored for patients who are predisposed to have *Candida* isolates with echinocandin resistance. Synovial and blood cultures should be obtained and processed for *Candida* species identification and susceptibilities to tailor antifungals and determine whether oral options for long-term therapy are available. Total duration of therapy is at least 6 weeks (see Table 23.5). For definitive therapy, if susceptible, the preferred antifungal is fluconazole, 400 mg (6 mg/kg) daily, for a minimum of 6 weeks. A less recommended option is an echinocandin for 2 weeks followed by fluconazole, 400 mg (6 mg/kg/day), for at least 4 weeks. A third option is the use of lipid formulation amphotericin B, 3–5 mg/kg/day for 2 weeks (which will give enough time for identification and an opportunity to obtain a susceptibility profile), followed by fluconazole (as outlined above) to complete 4 more weeks of therapy [52]. In the neonate, amphotericin B deoxycholate, 1 mg/kg daily, is the recommended therapy for disseminated candidiasis (limited data for lipid amphotericin B). Fluconazole, 12 mg/kg intravenous or oral daily, is an alternative in neonates that are not receiving fluconazole prophylaxis and are clinically stable. Lipid amphotericin B, 3–5 mg/kg daily can be used if there is no urinary tract involvement [52] (Table 23.6).

It is highly recommended to remove any prosthetic material in septic arthritis; however, if it cannot be removed, chronic suppression with fluconazole 400 mg (6 mg/kg/day) in a susceptible *Candida* species is an option (see

Table 23.5) [52]. If the triazoles are used, monitoring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin at baseline and every 1–2 weeks thereafter is recommended. Monitoring for amphotericin B (lipid or deoxycholate) should include a baseline serum creatinine, magnesium, phosphate, and daily in hospitalized patients, then twice weekly for outpatients. Monitoring for the echinocandins requires a baseline AST, ALT, and bilirubin and then every 1–2 weeks thereafter. In particular cases, to assist determining total duration of therapy for *Candida* arthritis, in association with clinical progression, serum BDG levels can be serially measured to monitor the response to therapy.

Prevention

Fluconazole prophylaxis, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily are recommended in adult intensive units with rates of *Candida* infections surpassing 5% [52], and some at-risk populations such as patients with solid organ transplants, patients with chemotherapy-induced neutropenia, patients with severe aplastic anemia, and stem cell transplant recipients. Fluconazole prophylaxis is supported by meta-analyses that have demonstrated a decrease in all-cause mortality, fungal-related death, and invasive fungal infection in adult oncologic patients after chemotherapy or hematopoietic stem cell transplantation. In general, these data can be extended to pediatric populations. In neonates, however, data is mixed; a randomized multicenter study of very low birth weight children (less than 1500 grams) found that fluconazole prophylaxis had a significant decrease in colonization and invasive candidiasis in comparison to placebo but did not have an impact in all-cause mortality [52, 53]. Ongoing research is exploring vaccine option(s) to prevent invasive candidiasis and mucosal candidiasis; however, no antifungal vaccine is available or expected in the near future. A major obstacle in the development of anti-*Candida* vaccine(s) is the existence of large genomic variation and phenotypic plasticity across *Candida* strains and species [106].

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Other Fungal Arthritis

24

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Introduction

There are around 100,000 species of known fungi, and about 150 are pathogenic to humans and animals; they can be challenging to identify and to define an appropriate therapy. Fungal arthritis and osteomyelitis are rare, and the causative agent often depends on the geographical location, occupation, sex, and social stratum, although today, with human mobility, these conditions can vary [1–3].

Osteoarticular infection can affect the joint cavity, bone, capsule, ligaments, tendons, and muscles, and its location is usually due to hematogenous spread but also by direct inoculation or contiguity from neighboring structures. It can affect primarily immunocompromised but sometimes immunocompetent patients; the most affected are those undergoing transplantation, chemotherapy for neoplasms, chronic granulomatous disease, AIDS, and autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) associated with debilitating conditions, disease activity, or the use of corticosteroids or immunosuppressants [4–6].

This topic is important since the diagnosis of fungal infections by health personnel is a challenge due to a low index of suspicion of fungal origin of osteoarticular infection, thus leading to late diagnosis with high morbidity and frequently devastating results. Herein, some other species are described.

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Aspergillus Species

Aspergillus is a ubiquitous, saprophytic but invasive fungus that can affect the lung. Pathogenic species include *A. fumigatus*, *A. niger*, *A. nidulans*, and *A. tubingensis* [7, 8]. *Aspergillus* species has a worldwide distribution, and its infection is frequently associated with debilitating conditions such as chronic granulomatous disease, solid organ or bone marrow transplantation, chemotherapy, intravenous drug use, diabetes mellitus, or malnutrition [7–9]. It has also been described in patients undergoing surgical interventions [8, 10, 11], immunocompetent individuals [12], and also in coinfection with tuberculosis [13, 14].

Aspergillus infection occurs through hematogenous spread, contiguous of a pulmonary foci in vertebral involvement, from chronic otitis in skull-base osteomyelitis, and lastly by inoculation in the case of surgeries or trauma [7, 8, 11–13].

Aspergillosis involves more males than females, with a median age of 50 years as demonstrated by Gameletsou et al. in 31 patients compiled by the International Consortium of Osteoarticular Mycosis, affecting both adults and children [8]. The most common clinical findings are pain and tenderness at the site of location, yet fever, edema, erythema, and decreased ranges of motion are rare. Most of the time the infection is monoarticular, predominately in knees and intervertebral joints and hips, among others. In the case of osteomyelitis, the tibia is the most compromised bone and juxta-articular osteomyelitis is common [8, 13]. Axial involvement is more frequent from a pulmonary foci; it often occurs with spondylodiscitis and can cause neurological deficit [2] (Figs. 24.1 and 24.2). Leukocytosis and neutrophilia may be present along with an elevation of acute-phase reactants. In synovial fluid, variable cell counts are described, mostly with a predominance of neutrophils [8].

Localized osteoporosis, joint space narrowing, lytic lesions, and adjacent periostitis can be observed [8, 10] with conventional radiography. Joint effusion, extension to neighboring soft tissues, increase in intensity signal in T2 and with

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_24

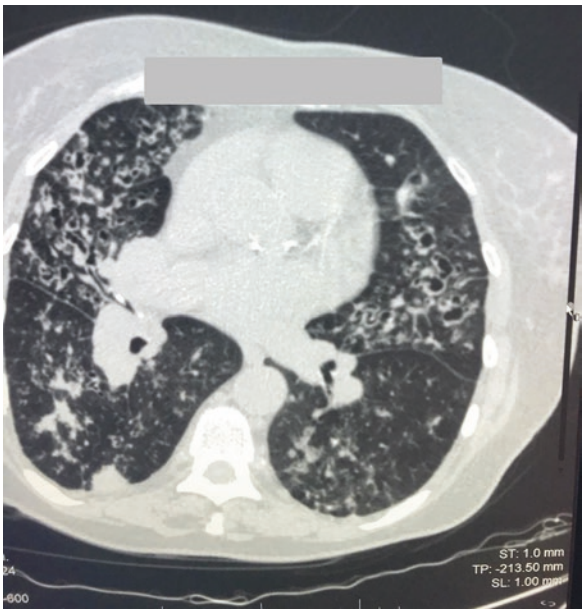

Fig. 24.1 Irregular thickening of interlobular septa, multiple micronodules, and irregular centrilobular distribution nodules with a ground-glass halo. Diffuse alteration of airway caliber conforming varicose bronchiectasis with some of them containing soft tissue due to aspergillosis. (Courtesy of Amalia Patiño MD, Radiologist. Clinica Las Americas)

contrast in T1, plus bone marrow edema can be demonstrated with magnetic resonance imaging [8, 9, 11, 12]. PET-CT can allow early diagnosis as well as treatment follow-up [7]. Arthrocentesis and open biopsy are the most commonly used methods for a definitive diagnosis of *Aspergillus* arthritis since fluid culture detects 100% of the cases; adjacent bone tissue culture is also highly sensitive [8]. In the histological study, about 50% of the cases are detected. With hematoxylin phloxine saffron stain, multinucleated giant cells with vacuolated cytoplasm are demonstrated [7]. Biomarkers such as galactomannan and β-D glucan and polymerase chain reaction are useful to establish a probable diagnosis [7, 15].

Cryptococcus Species

There are 19 cryptococcal species, but only two are pathogenic, *C. neoformans* and *C. gattii*; its life cycle is sexual and asexual. It has a worldwide distribution and is found in soil, in the feces of pigeons, and on trees such as eucalyptus [1, 3, 16]. *Cryptococcus gattii* is an emerging pathogen in the northwestern region of the United States and in western Canada [1].

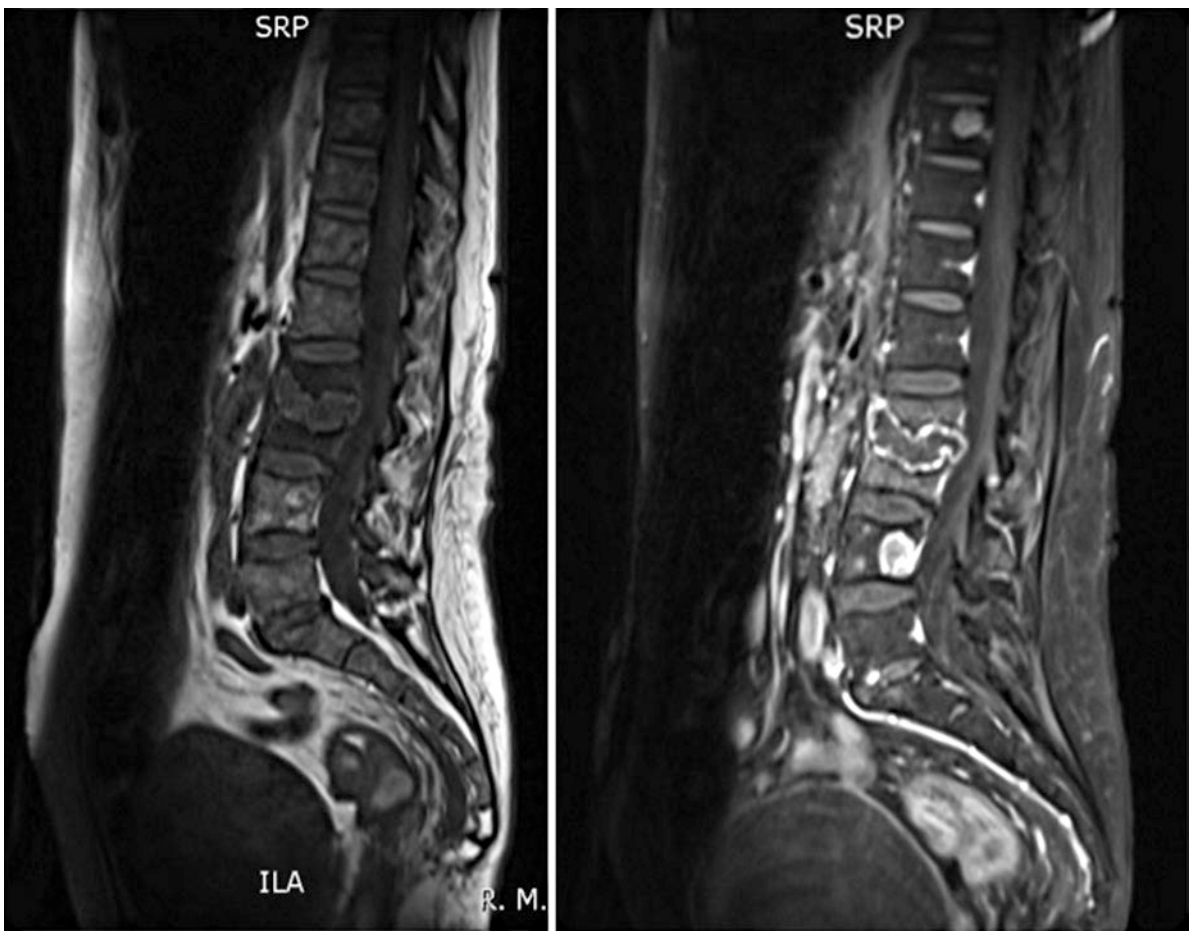

Fig. 24.2 L3 and L4 decreased height, hypointense in T1 that intensifies with contrast in SPIR. There is also an increase of the L3-L4 disc, enhancing due to spondylodiscitis. In the L4 vertebral body, there is another round image that magnifies and could have an infectious origin, by *Aspergillus*. (Courtesy of Isabel Ramirez MD, Infectious Disease. Hospital Pablo Tobon Uribe)

Cryptococcus is usually acquired by means of inhalation and occasionally secondary to trauma or inoculation through the gastrointestinal tract [1]. Three factors determine its pathogenicity: host defense, virulence of the strain, and inoculum size, but generally cryptococcosis is considered a relapsing disease [1, 14, 16]. It has a hematogenous dissemination in immunosuppressed patients, such as recipients of solid organ or bone marrow transplantation, with neoplasms undergoing chemotherapy, sarcoidosis, AIDS, or in autoimmune diseases such as SLE with high disease activity, corticosteroid use, and in RA with employment of biological agents against tumor necrosis factor [4, 6, 14–21], but it has also been described in immunocompetent subjects [22].

Cryptococcus, after *Candida* and *Aspergillus*, is the most common fungal infection, and its spread generally causes meningoencephalitis, pneumonia, pulmonary nodules, and kidney and skin involvement which can manifest as papules, nodules, acneiform lesions, ulcers, and cellulitis [22, 23] (Fig. 24.3). Osteoarticular infection is very rare since the number of reported cases is very low [16, 17, 20, 22, 24], and osteoarticular infection by *C. gattii* has not been described [2]. Osteoarticular infection can be subacute/chronic and produces evident inflammatory symptoms such as warmth, redness, edema, functional impairment, and joint effusion. In only 10–20% of cases, it is associated with osteomyelitis, the ribs, skull, pelvis, epiphysis of long bones, and vertebrae being the most affected. Tenosynovitis and myositis have also been reported [18, 19, 21, 25] (Table 24.1).

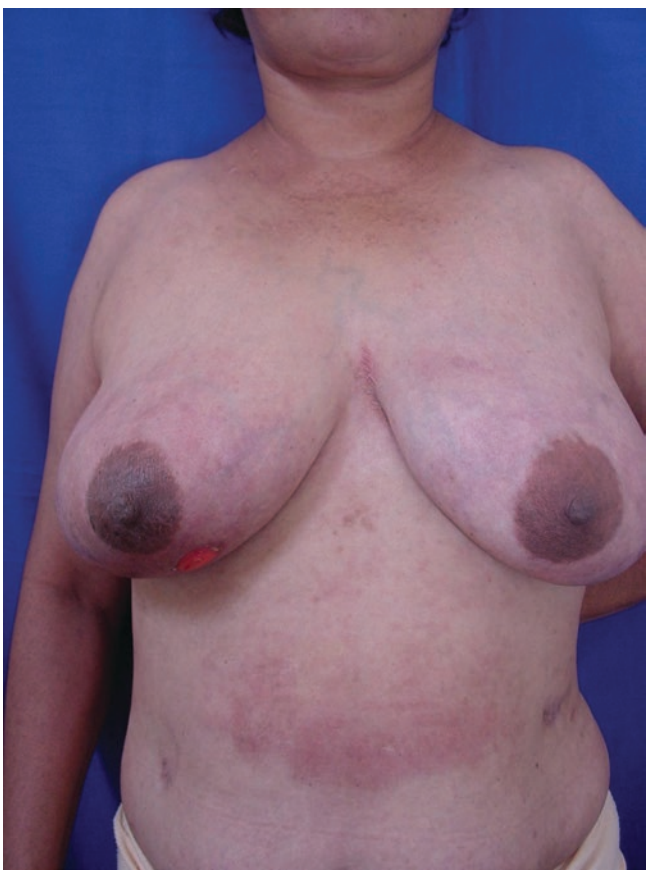

Fig. 24.3 Lupus patient with skin lesions: ulcers and papules due to cryptococcosis

Laboratory findings include both C-reactive protein and erythrocyte sedimentation rate elevation. The joint fluid may be turbid or purulent in appearance with variable cellularity but predominantly mononuclear, and the culture should always be searched for the germ on Sabouraud glucose agar with chloramphenicol. Blood and cerebrospinal fluid cultures should also be taken, as well as cultures of urine and other compromised tissues [18, 19, 21, 23, 25]. When *Cryptococcus* isolation is performed, lumbar puncture is necessary to rule out central nervous system involvement [21].

Another important aid is the detection of the blood antigen that can be done by latex agglutination or ELISA, being almost as sensitive as the isolation of the fungus, which does not happen with the detection of the antibody [21]. Another diagnostic aid is a biopsy in which stains are used, such as hematoxylin and eosin, methenamine silver, or PAS that enable yeast identification and also reveal acute and chronic inflammation with giant cell granulomas without caseification [18, 26] (Fig. 24.4).

Conventional radiological images can be normal or show osteopenia and erosive and frankly lytic lesions with diminution or loss of joint space and periosteal elevation, depending on the time of evolution [19, 23, 25, 26]. Magnetic resonance imaging can demonstrate soft tissue masses in T1 with gadolinium and fat suppression, bone edema with a focal replacement of the bone marrow, and increased intensity in tendons and muscle, with tendon thickening [19, 21].

Finally, it is necessary to draw attention to the importance of thinking about fungi as responsible for osteoarticu-

Table 24.1 Clinical characteristics in 25 patients with cryptococcal arthritis

Average age	42.16 years	
Sex	Female	9
	Male	15
	ND	1
Underlying disease	None	3
	Present	21
	ND	1
Immunosuppressants	Yes	10
	No	14
	ND	1
Involved joint	Knee	12
	Ankle	4
	Elbow	3
	Polyarthritis	3
	Other	5
	ND	2
Osteomyelitis		10
Joint Isolation		22

ND No data
Data from Refs. [18–21, 24, 25]

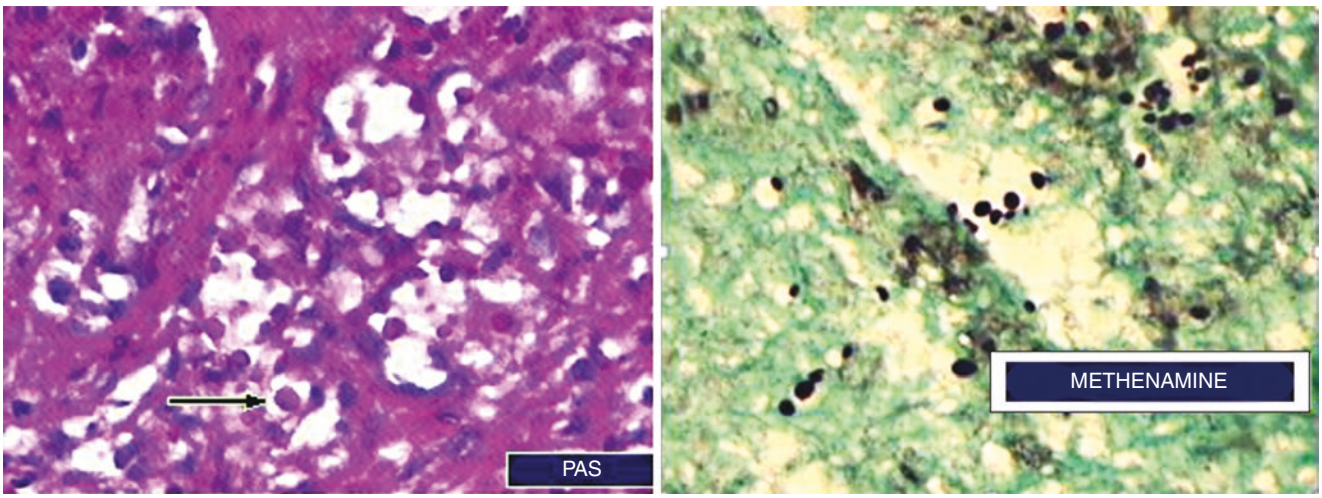

Fig. 24.4 Cryptococcus tissue demonstration with different stains. 400×

lar infection in predisposed patients as described earlier, in order to achieve a timely diagnosis, improving joint prognosis and survival.

Sporotrichosis Arthritis

It is a subacute/chronic mycosis caused by *Sporothrix schenckii*, of which five species capable of producing infection in humans have been described: *S. schenckii* sensu stricto, *S. brasiliensis*, *S. globosa*, *S. mexicana*, and *S. luriel*. It has a worldwide distribution and is found on soil and plants. It is a dimorphic fungus, which mostly involves men working in gardening, construction, mining, or peasants [27–30]. The first cases were reported in the USA, and later in France [29, 30].

Acquisition has not been totally elucidated, yet it is thought to be by inoculation secondary to trauma (even minimal), by cat scratch, contamination of soil or organic material, and even rose thorns [30–32]. It is assumed that the inhalation route is possible, when there is no evidence of trauma [33]. Sporotrichosis generally presents in alcoholic patients, diabetics, immunosuppressed by AIDS, use of corticosteroids or biological agents, myelodysplasia, neoplasia, organ transplantation [30, 34–41], and even in immunocompetent subjects [29, 31, 32, 39, 42–44].

Patients who undergo osteoarticular involvement do not regularly present significant systemic symptoms and have an indolent course [28, 31, 32, 35, 38]. The most frequent clinical affection is determined by the findings in the skin that can appear as painful nodules, sometimes with erythema or ulceration with or without exudate, or late with fistulous trajectories [34, 35, 39, 41]. More rarely, erythema nodosum has been described [41]. A finding that has been described as characteristic is a lymphangitic spread [29, 31] (Fig. 24.5). Another type of compromise is given by cervical or axillary satellite lymph nodes [28, 41]. Pneumonitis and meningitis have also been described.

Osteoarticular compromise is a late diagnosis, because clinicians rarely think *Sporothrix schenckii* as a cause of chronic arthritis that manifests with pain, erythema, functional impairment, with joint effusion and destruction, localized osteoporosis, and lytic lesions causing great morbidity [27, 29, 37, 44]. There is also bursal, tenosynovial, and muscle involvement [27, 40, 43, 44] (Figs. 24.6 and 24.7). This osteoarticular affection is rare, comprising 2–4% of all cases of sporotrichosis, and even more exceptional as an isolated clinical manifestation [30]; therefore, it is postulated that *Sporothrix schenckii* may have a hematogenous spread after inhalation, and it has also been isolated in the blood [37, 45]. Arthritis is more frequently monoarticular, although, as can be seen in a compilation of 19 cases, 10 were monoarticular and 8 were polyarticular; the most affected joints were knee (13), wrist (9), elbow (5), and ankle (2), among others, and there was concomitant osteomyelitis in 4 patients and only in one case, it was isolated (Table 24.2). The delay in diagnosis ranges from 3 to 96 months [33].

Laboratory studies are not very specific; the most striking feature is a high erythrocyte sedimentation rate, as well as C-reactive protein elevation. Synovial fluid is usually inflammatory or serohematic, with a predominance of neutrophils or lymphocytes. In this case, as well in the biopsies, the presence of the fungus is scarce, which also makes the diagnosis

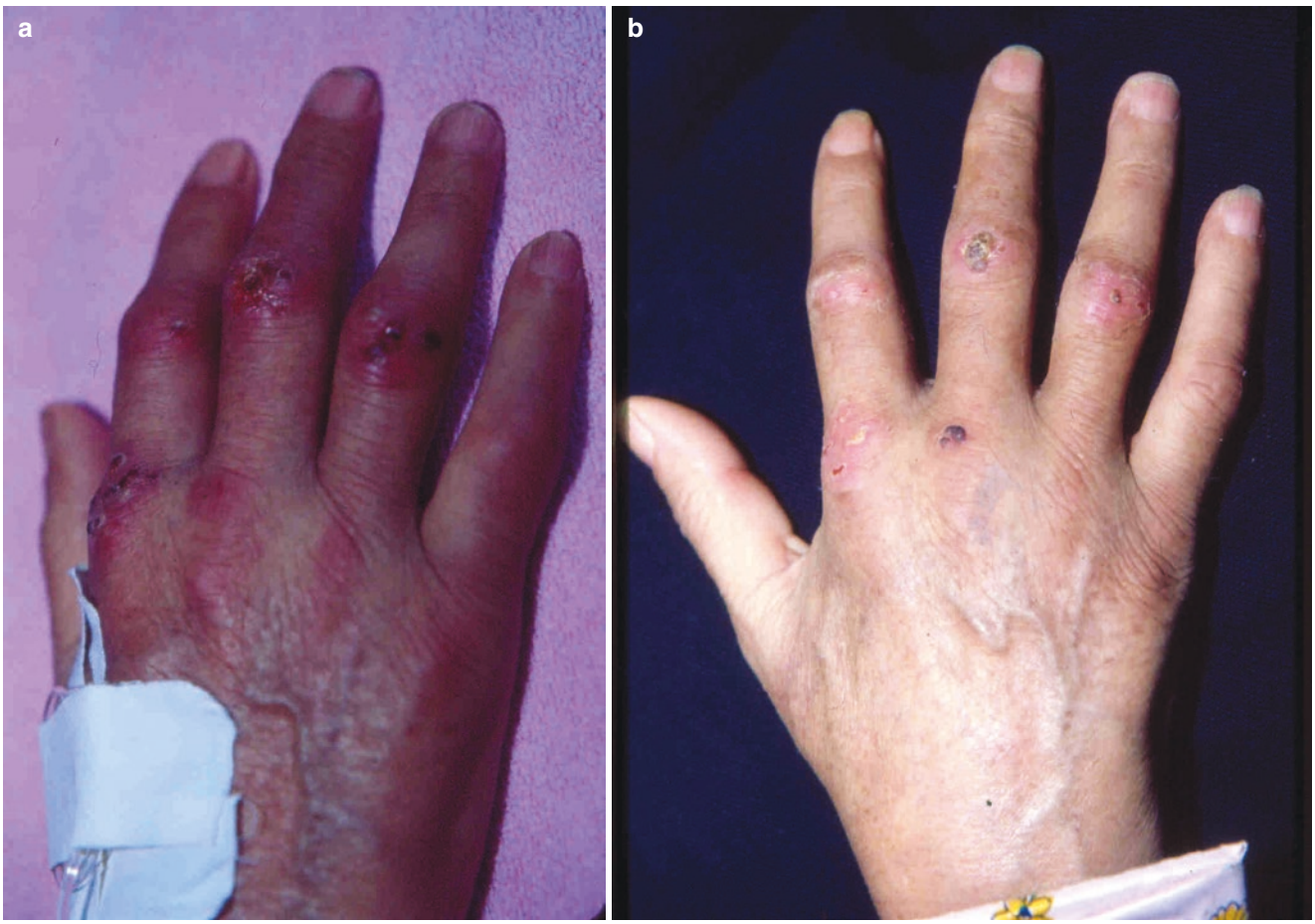

Fig. 24.5 (**a**) Papulovesiculosis lesions in early sporotrichosis; note the proximal interphalangeal arthritis. (**b**) Scarring lesions after treatment with itraconazole. (Courtesy of Oscar Uribe MD. Rheumatologist)

difficult [27, 40]. Serology for sporotrichosis has been used, employing ELISA with a fraction of SsCBF antigen, which is recognized by IgG antibodies and has shown a sensitivity of 90% and a specificity of 80% [42].

The gold standard for diagnosis is the culture, whether in synovial fluid, tissue samples, exudates of ulcers, and, occasionally, blood (see Table 24.2). The culture is done in Sabouraud dextrose agar [28, 30]. The biopsy shows granulomas with a central area of necrosis surrounded by multinucleated giant cells and palisaded histiocytes, but sometimes it does not have central necrosis which makes it indistinguishable from sarcoidosis. Although nonspecific and infrequent, oval bodies with a cigar shape and occasionally yeasts can be observed. The employed stains are glycol methacrylate, silver methenamine, or hematoxylin-eosin; asteroid bodies can also be observed [30, 40, 43, 44].

Conventional radiography is the most useful technique due to the chronic disease progression, demonstrating juxta-articular osteoporosis, soft tissue edema, diminution or loss of joint space, erosions, lytic bone lesions, periostitis, and great joint destruction [35, 38, 39]. Occasionally ultrasound, computed tomography, or magnetic resonance is used [29, 30, 40].

Paracoccidioidomycosis

Paracoccidioidomycosis is a disease that can be acute/subacute or chronic which is caused by *Paracoccidioides brasiliensis* and *P. lutzii*. It is a dimorphic fungus identified by multiple yeasts in what has become known as " pilot's wheel" [47]. Its study began in Brazil in 1908, when Lutz reported the first two patients, isolating the germ, and later described by Splendore, but it was not until 1930 when Almeida determined that it was a fungus and gave it its current name [48].

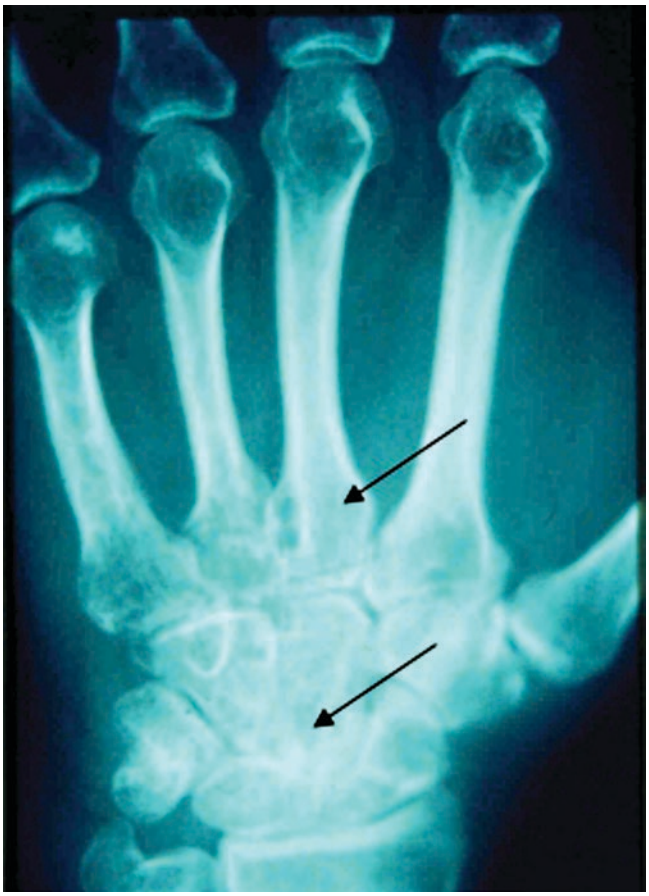

Fig. 24.6 Approach showing radiolucent lesions at the base of the third metacarpal and loss of intracarpal spaces with multiple radiolucent lesions by sporotrichosis. (Courtesy of Oscar Uribe MD. Rheumatologist)

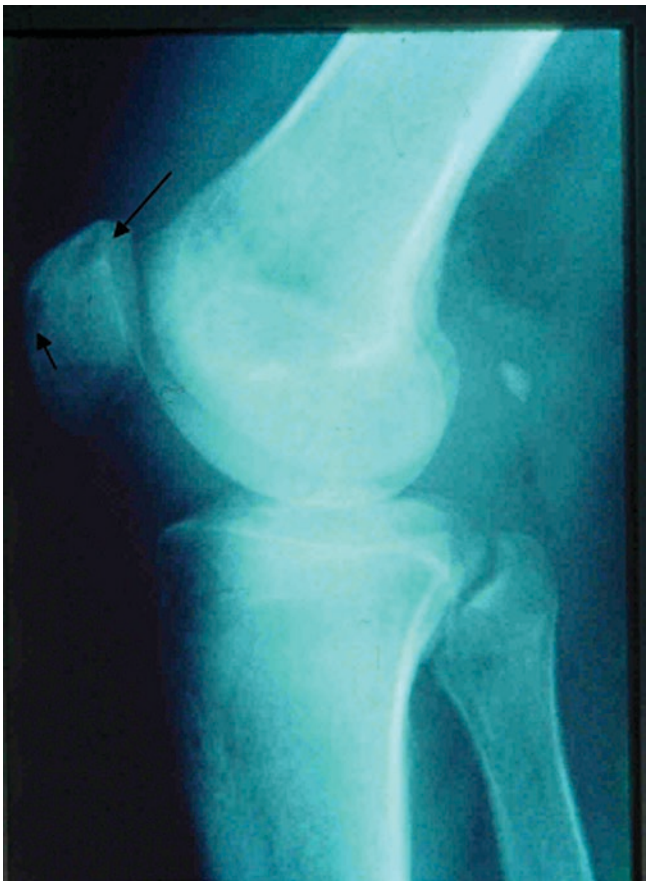

Fig. 24.7 Lateral knee X-ray demonstrating radiolucent lesions in the patella by sporotrichosis. (Courtesy of Oscar Uribe MD. Rheumatologist)

Paracoccidioidomycosis is the most frequent systemic mycosis in Latin America from Mexico to Argentina, with a high endemicity in Brazil, so that the cases described in other countries are imported due to the current high mobility [48, 49]. Approximately half of the described cases occur in rural areas, including landowners and agricultural workers; however, they have also been described in construction workers and generally occur in humid tropical and subtropical forest areas [48, 49].

The infection occurs through inhalation of the saprophytic fungus that is found in soil and plants and can be located in the lung where the human tissue can surround it or produce clinical involvement and disseminate hematogenously, affecting the skin, mucous membranes, reticuloendothelial system, gastrointestinal tract, central nervous system, osteoarticular system, genitals, and suprarenal glands [50–52]. This fungus' behavior has been associated with smoking, alcoholism, tuberculosis, chronic obstructive pulmonary disease, AIDS, and neoplasms [49].

The most common form of clinical presentation is chronic (75%), predominantly in males in a 6:1 ratio with respect to females; the average age is 40.8 years and is characterized by pulmonary involvement [49]. The acute/subacute form has no predilection for gender and is more common in children and adolescents with multisystemic manifestations: adenopathies, hepatosplenomegaly, skin lesions (papules, nodules, or ulcers), lung and osteoarticular involvement, as well as severe conditions of the general state with fever and anemia [50, 51].

Osteoarticular compromise is more predominant in the acute/subacute type and is occasionally observed in the chronic form. Most of the lesions are seen in long bones, involving metaphyses, clavicles, ribs, scapula, skull, and vertebrae [50–52]. Arthritis has been described affecting the hip, knee, shoulder, wrist, and small hand joints as acute or, very rarely, chronic manifestations [52–54]. It may cause myositis and has been described to be associated with rheumatoid arthritis [54, 55].

Table 24.2 Clinical characteristics of 19 patients with osteoarticular infection by *Sporothrix schenckii*

Reference	Age	Sex	Background	Joint pattern	Joint	Osteomyelitis	Fungus isolation
[27]	34	Male	Alcoholism	Poly	Wrist, elbow, knee	Yes	Bone
[28]	53	Female	Diabetes	Mono	Knee	No	Skin and joint fluid
[29]	74	Male	None	Mono	Wrist	Yes	Skin
[30]	33	Male	Alcoholism	Mono	Knee	No	Synovium, joint fluid
[31]	31	Female	None	Poly	Ankles, elbows	No	Skin
[32]	47	Male	None	Mono	Knee	No	Joint fluid
[32]	35	Male	None	Mono	Knee	Yes	Joint fluid
[34]	48	Female	Diabetes	–	None	Yes	Bone, skin
[35]	55	Male	Alcoholism	Poly	Wrist, elbow	No	Joint fluid
[36]	59	Male	Alcoholism	Mono	Knee	No	Joint fluid
[37]	60	Male	Alcoholism	Poly	Wrist, knee	Yes	Joint fluid, blood, skin
[38]	49	Male	Alcoholism	Poly	Wrist, elbow, knee, ankle	No	Joint fluid
[42]	88	Female	None	Mono	Knee	No	Joint fluid, synovium
[40]	72	Male	Ulcerative colitis and corticosteroids	Mono	Wrist	No	Synovium
[41]	51	Male	Diabetes	Mono	Knee	No	Joint fluid
[46]	49	Male	Immunosuppressants and alcoholism	Mono	Knee	No	Skin
[45]	78	Male	Immunosuppressants	Poly	Wrist, knee, shoulder, MCP, PIP	No	Blood
[43]	49	Female	None	Poly	Wrist, elbow	No	Synovium
[44]	50	Male	None	Poly	Wrist, knee	Yes	Joint fluid

MCP Metacarpophalangeal joint, *PIP* proximal interphalangeal joint

Laboratory studies can reveal anemia, leukocytosis (sometimes with eosinophilia), and elevation of erythrocyte sedimentation rate and C-reactive protein. In conventional radiography, lytic lesions without or minimal sclerosis are observed, single or multiple, and typically without periostitis [50–52]. Ultrasound has been used when there is soft tissue involvement, with the demonstration of tenosynovitis and intense signal in power Doppler [53]. Magnetic resonance imaging is described as a high-intensity signal that enhances with gadolinium, bone edema, and the penumbra sign in T1, similarly to other conditions that cause abscesses, findings that can be useful to differentiate it from neoplasms; none of these are characteristic of the entity [54].

Diagnosis is based on the identification of the fungus, either by direct microscopic examination or histopathology [47]. IgM and IgG antibody detection (serological study) has also been used, applying different techniques such as gel immunodiffusion, complement fixation, ELISA, or counter-immunoelectrophoresis. Complement fixation and ELISA have the limitation of cross-reacting with histoplasmosis [56]. Bellissimo-Rodrigues et al., in 1000 patients, found that counterimmunoelectrophoresis was positive in 97.2% and histopathology in 64.7%, while the culture of the fungus was only positive in 25.3% of the subjects [49]. Pathological anatomy reveals a granulomatous reaction with epithelioid and giant cells using silver methenamine or hematoxylin-eosin stains, allowing yeast identification [55, 57] (Figs. 24.8 and 24.9).

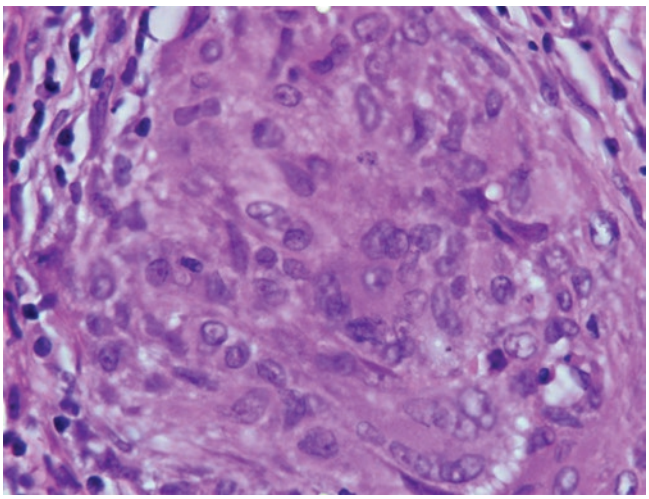

Fig. 24.8 Granulomatous inflammation with multinucleated giant cells due to paracoccidioidomycosis. Hematoxylin stain, 400×

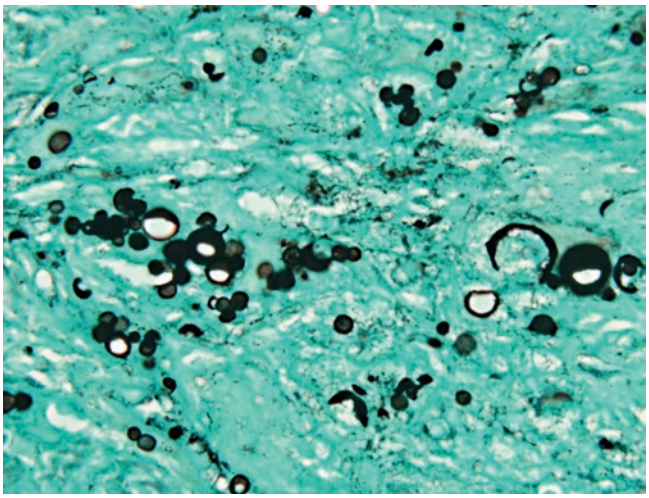

Fig. 24.9 Large, round yeast cell with multiple narrow-based budding yeast (paracoccidioidomycosis). Silver methenamine, 400×

Bone and Joint Infections Caused by Mucormycetes

Mucormycosis is a rare infection caused by filamentous fungi of the *Mucorales* order, previously called zygomycosis. The *Mucorales* are fungi of worldwide distribution, whose predominant pathogenic genera include *Rhizopus* species, followed by *Mucor*, *Rhizomucor*, and *Lichtheimia*, among others [58–60]. They are saprophytic and can be found in soil, decomposing materials, wastewater, decomposed plants, bread mold, and garbage. They are acquired by inoculation after trauma (even minimal), penetrating injuries, surgical procedures, and arthrocentesis [59, 60].

This infection is more commonly found in immunocompromised patients, such as diabetics, neutropenic, neoplasms in chemotherapy, solid organ or bone marrow transplantation, use of corticosteroids, systemic lupus erythematosus, rheumatoid arthritis treated with TNF blockers, and AIDS [2, 60–64]; however, it has also been described in immunocompetent individuals [65]. Diabetic patients, especially with ketoacidosis, have a greater predisposition since metabolic acidosis increases the pathogenic potential of the fungus by altering iron clearance [58].

This bone and joint infection predominates in men, corresponding to 71% in a series of 34 patients. It affects adults and children, and the average time for diagnosis was 73 days, being more indolent than other types of affection [60]. Skin involvement is more common on the face, cheeks, and periorbital region but can affect other body areas. It can present as papules, painful subcutaneous nodules, necrotic crusts, ulcers, fistulas, and abscesses. It is locally very invasive and can spread by contiguity or hematogenously to affect the central nervous system (rhinocerebral mucormycosis), lungs, gastrointestinal tract, or osteoarticular system

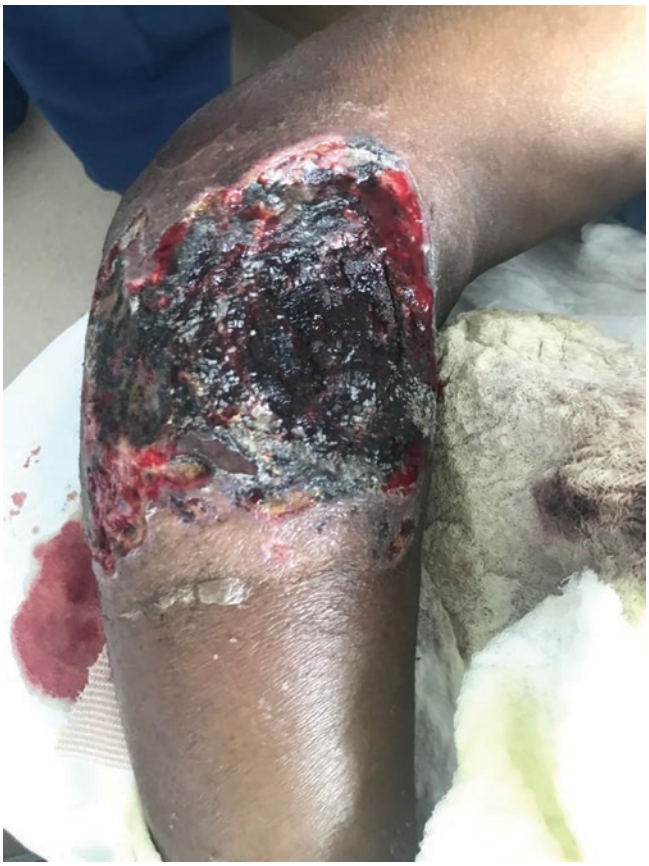

Fig. 24.10 Great ulceration with necrotic crust on the forearm due to mucormycosis

[59–62] (Fig. 24.10). Joint involvement manifests with pain, decreased range of motion, and edema which are predominant findings. The most involved joints are the hip, knee, and ankle, while osteomyelitis affects the tibia, femur, maxilla, vertebrae, skull, and humerus, among others [58–60].

Leukocytosis can be found, as well as elevation of acute-phase reactants, but the most important diagnostic aid is a skin biopsy with hematoxylin-eosin, methenamine silver, and/or PAS stains, showing suppurative granulomas suggestive of infectious panniculitis in the deep dermis and subcutaneous fat. Angioinvasive hyphae are also demonstrated in the light or wall of vessels, causing thrombosis and necrosis responsible for the aggressiveness of the affection. Such hyphae are large, broad, and not-septated and branch at right angles, unlike those of *Aspergillus* that do so at an acute angle, which is sufficient to prove the presence of the fungus [58, 62, 63]. Calcofluor white stain reveals up to 80% the presence of hyphae and allows their differentiation between septate and non-septate with 5% of false positives [66]. Culture in a non- selective medium allows identification of the germ with rapid growth [58]. There are still no biomarkers available for the diagnosis of mucormycosis [63, 66].

Imaging studies are important since multiple types of injuries can be observed, including lytic, erosive, and destructive with conventional radiography. Magnetic resonance imaging shows low-intensity signal in T1 and high-intensity patches in T2, enabling detection of invasion of neighboring tissues, which is why it is preferred over CT. Ultrasound and CT are used to take guided samples [58, 66].

Finally, it can be noted that joint and bone infections caused by *Mucorales* have been increasing in frequency since the number of patients at risk is rising. It is important to highlight the aggressiveness of this infection due to its capacity to cause angioinvasion with extensive tissue damage which makes early diagnosis mandatory, along with aggressive medical and surgical treatment to reduce its high morbidity and mortality.

Treatment

There are no controlled studies for the treatment of these bone and joint infections, given their low frequency. The management applied is based on the results of case series presentations although more recently there are recommendations from international societies for mucormycosis [66], sporotrichosis [67], and cryptococcosis [68], but are not centered in osteoarticular infection. Therefore, this management is extrapolated and adapted to individual conditions of the patient.

Treatment, in general, involves prolonged medical management with antifungal agents. In the surgical aspect, debridement of soft tissues, arthrotomy, bone curettage, removal of osteosynthesis material or joint prosthesis, and even amputation in some cases must be performed. Medical and surgical management results in better survival [1, 7, 8, 19, 21, 26, 39, 54, 58, 61, 63].

The drug most commonly used as a first option is amphotericin B with liposomal formulation (4–6 mg/kg IV) which has fewer side effects, such as renal failure and hypokalemia, compared to deoxycholate (0.5–1.0 mg/kg/day IV), the use of which should be discouraged [66, 67]. It should be noted that all treatments initiated with amphotericin B, after obtaining a good response, are continued with other medications such as itraconazole 200 mg bid PO. In the case of sporotrichosis, treatment is continued for up to 12 months, during which it is recommended to determine serum levels after two weeks of use to ensure adequate exposure to the medication [67] (Table 24.3).

For cryptococcosis, the recommendation is amphotericin B plus 5-flucytosine for 3–6 weeks as consolidation therapy, followed by fluconazole 400 mg/day for 10 weeks and then 200 mg/day for 12 months. The alternative is itraconazole 200 mg bid PO for individuals intolerant to fluconazole [21, 68].

For aspergillosis, the recommendation is voriconazole, which may be superior to amphotericin B initiated with an IV loading dose of 6 mg/kg bid for the first day and continued with 4 mg/kg/day bid for 3 more days. Afterward, it is switched to 100–150 mg bid PO 1 hour after or before a meal, achieving suitable concentrations both in synovial fluid and blood, yet monitoring of blood drug concentrations is required. The duration of treatment should be 6–12 weeks; however, it should always be individualized according to the

Table 24.3 Antifungal treatment in osteoarticular infection

Fungus	Medicine	Dose	Adverse effects
Aspergillosis	Voriconazole Ampho B lipo Anfo B DHC	4 mg/kg/d 4–5 mg/Kg/d 0.5–1 mg/Kg/d	Fever, AST and ALT elevation, cholestasis, rash, hypokalemia, anaphylaxis, chills
Cryptococcosis	Ampho B plus 5-flucytosine; then fluconazole	*Idem*	*Idem*
		50–150 mg/Kg/d 400 mg; then 200 mg/d PO	Rash, pruritus, elevated creatinine
		Children: 6–12 mg/kg/d	Nausea, vomiting, rash, AST and ALT elevation
Sporotrichosis	Ampho B; then itraconazole	*Idem*	*Idem*
		200 mg bid PO	Nausea, vomiting, AST and ALT elevation, myalgias, anxiety
Mucormycosis	Ampho B plus caspofungin or posaconazole	*Idem*	*Idem*
		50 mg IV/d > 13 years: 300 mg/d PO	Fever, diarrhea, AST and ALT elevation, fever, chills, vomiting, diarrhea, fatigue, myalgias, AST and ALT elevation
Paracoccidioidomycosis	Itraconazole	600 mg/ d for 3 days; then 200 mg/d	*Idem*
		Children: 5 mg/Kg/d	Leukopenia, anemia, rash
	TMP-SMX	TMP: 160–240 mg/d; children: 8–10 mg/Kg/d SMX: 800–1200 mg/d Children: 40–50 mg/Kg/d	

Ampho B lipo Liposomal amphotericin B, *Ampho DHC* deoxycholate amphotericin B, *ARF* acute renal failure, *PO* oral route, *TMP-SMX* trimethoprim-sulfamethoxazole
Data from Refs. [8, 21, 47, 54, 58, 63, 67, 68]

severity of involvement and the degree of immunosuppression of the patient as with any fungal treatment [21]. Amphotericin B followed by itraconazole has also been used [8].

In mucormycosis, the drug of choice is amphotericin B in the liposomal formulation, and, in some cases, it has been recommended to combine it with caspofungin [58]. Posaconazole with delayed release has also been employed [58, 63].

The treatment of choice for paracoccidioidomycosis is itraconazole 600 mg/day for 3 days followed by 200 mg/day for 6–9 months. Amphotericin B, voriconazole, or trimethoprim/sulfamethoxazole has also been used [47, 54].

Conclusion

In conclusion, the cornerstone for proper treatment of these bone and joint infections is that clinicians keep in mind to facilitate early diagnosis, which is not easy due to the scarcity of their occurrence, in addition to their torpid evolution (except for mucormycosis), and the necessary installation of aggressive diagnostic and therapeutic procedures to reduce morbidity and mortality.

Acknowledgments

Special thanks to Amalia Patiño MD (Clínica Las Américas), Isabel Ramírez MD (Hospital Pablo Tobón Uribe), and Oscar Uribe MD (Universidad de Antioquia) for giving us the clinical and radiological figures of Aspergillus and sporotrichosis, respectively.

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Syphilis-Related Musculoskeletal Manifestations

25

Najia Hajjaj-Hassouni and Hanan Rkain

Introduction

Syphilis is a chronic sexually transmitted infection due to the spirochetal bacterium *Treponema pallidum* (TP) subspecies *Pallidum* which affects each year about 12 million new people in the world [1]. Despite active preventive campaigns in the early 1980s, the overall incidence of sexually transmitted diseases (STD), among them acquired immune deficiency syndrome (AIDS) and syphilis, remains high in the world. Syphilis is still an important disease for health care providers particularly in light of its worldwide increasing rates since 1980 [2]. In low-income and middle-income countries (LMICs), syphilis is responsible for a high morbidity including adverse pregnancy outcomes and acceleration of human immunodeficiency virus (HIV) transmission [3]. In sub-Saharan Africa, for instance, syphilis (but also non-venereal treponematosis yaws, bejel, and pinta) declined significantly and then stabilized as a result of penicillin benzathine mass treatment campaigns initiated between 1954 and 1963 by the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) [4]. In western countries, syphilis had declined sharply since the discovery of penicillin in 1945. However, these countries are also experiencing resurgences of AIDS-related syphilis since the 2000s, particularly among men having sex with men (MSM) [5–7]. Increased incidence amongst MSM is associated with the use of illicit drugs and an increased transmission of HIV because of a decreased vigilance since AIDS triple therapy. Moreover, syphilitic genital ulcers are infiltrated with lymphocytes, the primary target cells for HIV infection, providing thus a portal of entry for HIV acquisition [2]. This increasing trend of syphilis has also been recently reported in childbearing-aged women, leading thus to new cases of congenital syphilis [8, 9]. Moreover, it has been demonstrated that STD, among them syphilis, not only indirectly facilitate the sexual transmission of HIV but are also considered responsible for cellular changes that precede some cancers [1]. The natural history of acquired syphilis is stereotyped with a three-phase clinical evolution: primary (chancre), secondary (treponemal sepsis, until the 5th year) and tertiary (mucocutaneous, neurological and cardiovascular complications). A latent phase (early and late) takes place between the secondary and the tertiary phase. Thus, recent syphilis includes primary, secondary, and latent syphilis less than 1 year from primary exposure, referred to as "infectious syphilis," and late syphilis which includes tertiary syphilis and latent syphilis of more than 1 year [2]. In the latter, the major consideration shifts to personal morbidity including late neurosyphilis and cardiovascular and gummatous infections [2]. Investigations are mainly based on serological tests. They include non-specific tests (non treponemal) like venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR) and specific (treponemal) tests such as enzyme immunoassay (EIA), enzyme-linked immunosorbent assay (ELISA), and fluorescent treponemal antibodies absorbed IgM (FTA-ABS) tests, more sensitive and automated than the classical *Treponema pallidum* particle agglutination (TPPA) [2]. Penicillin remains the drug of choice for all stages of infection. Syphilis is mainly a mucocutaneous expression disorder, at least at its early stages. However, the natural history of the disease includes not only the central nervous and the cardiovascular systems but also many other sites among them, the musculoskeletal system. Musculoskeletal manifestations (MSKM) of syphilis, although rare, should be kept in mind because of the recrudescence of the disease and because of their frequently misleading expression which contributed to making the disease earn the name "great simulator." Syphilitic MSKM are related to the hematogenous dissemination of TP [2]. The main lesions are bone involvement and arthritis, the pattern of which is in keeping with the clinical presentation of the disease. However, involvement of muscles, tendons and their sheaths, as well as bursitis, although rare, have also been

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_25

reported. MSKM in secondary or tertiary acquired syphilis as well as in congenital syphilis will be reported. In the latter, lesions can be early, mainly between the birth and the fourth month but up to the age of 2 years, or late, between 6 and 12 years old, giving at this stage nearly the same lesions as those of tertiary acquired syphilis. MSKM of late congenital syphilis will therefore be described with tertiary acquired syphilis.

Early Congenital Syphilis

In spite of preventive measures and effective and relatively inexpensive treatments, the burden of congenital syphilis remains underestimated mainly in LMICs [10] and is also reported again in developed countries [8]. In LMICs, syphilis incidence in pregnant women can be as high as 17% [8]. The mother-to-fetus transmission is usually caused by transmission of TP across the placenta from the fifth month of life in utero. Infection may also occur, although exceptional, during birth. When it occurs (18–50% of infected mothers), infection is responsible for a high mortality (abortion, stillbirth, death of live neonates) and for congenital syphilis in remaining live newborns [8]. In untreated infection, as reported in LMICs, bone involvement occurs in about 65% of the cases, particularly with systemic organ involvement of the disease [11, 12]. At the very early stage, bone involvement may be asymptomatic and discovered only on X-ray [11]. The lesions mainly concern the long bones' metaphysis, particularly the femur and the tibia to the vicinity of the knee, as well as the humerus, near the shoulder. They may more rarely involve metacarpals and phalanges as well as the ribs, the flat bones and the skull. The usual patterns, present in 23–57% of patients, symmetrically organized, singly or in combination, are osteochondritis, periosteitis, or osteitis [11, 12]. Chondritis lesions can concern one or even all the four limbs. Early X-ray shows an enlargement and thickening of the metaphysis with irregularities of the ossification line (stage 1, Fig. 25.1) and one or more clear metaphyseal bands which may realize alternating dense and lucent bands (stage 2, Fig. 25.2) [13]. At a further stage, the ossification zone disappears and is replaced by deep symmetrical erosions at the inner edge of the involved metaphysis, which may contain sequestra, known as Wimberger's sign (stage 3, Fig. 25.3) [13, 14]. This leads to the displacement of the epiphysis and severe painful motor impotence. When the four limbs are concerned, this leads to a pseudo-paralytic functional impotence realizing the so-called Parrot pseudo-paralysis. At a further stage, the occurrence of a fracture at the weakened site of the bone will cause severe pain (stage 4, Fig. 25.4) [13]. Chondritis may also be responsible for rhinitis, destruction of nasal cartilage and laryngeal involvement that may produce laryngitis, snoring or hoarse crying [8, 15]. Ossifying

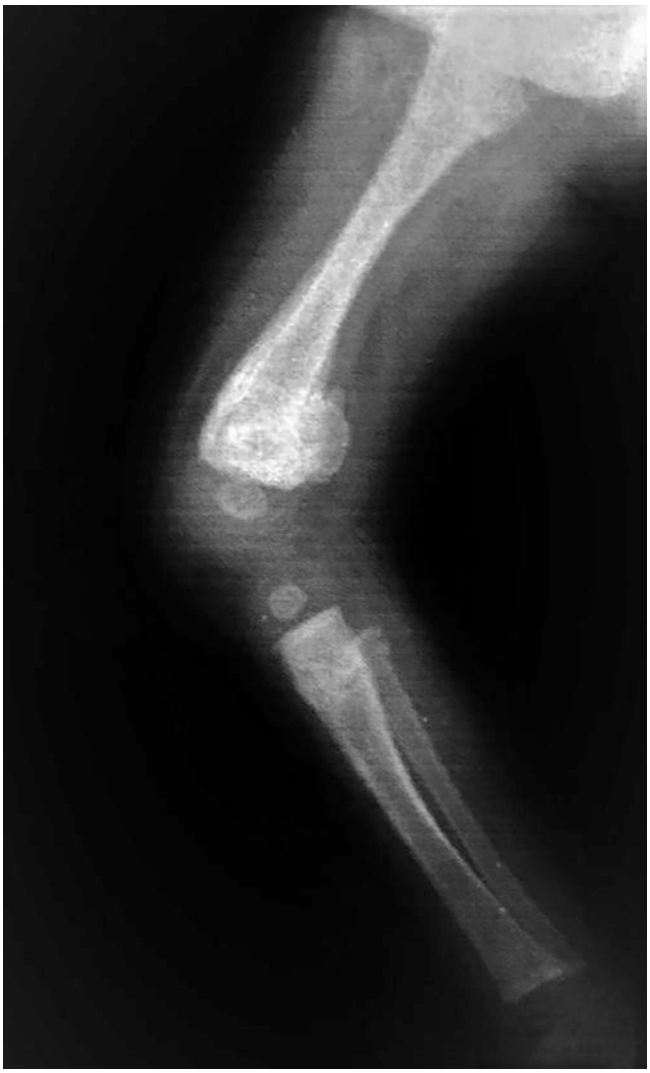

Fig. 25.1 Enlargement and thickening of the femur and tibia metaphysis, stage 1. Exuberant bone neoformation developed at the end of the femur. (From Benyaich [13], reprinted with permission)

periosteitis may be responsible for swelling of the affected limbs but often remains asymptomatic and therefore fortuitously discovered on X-ray in about 30% of the children [11, 12]. Ossifying periosteitis appears in the first 6 months or even in utero. Lesions are diffuse and symmetrical. They may concern all the bones even if the long bones are more often concerned, particularly at the inner side of the shins. The periosteal and cortical diaphyseal bone is thickened and doubled with lamellar subperiosteal bone neoformations which give to the bone wall a laminated appearance (Fig. 25.5) [13]. Even without treatment, these lesions disappear at the age of about 1 year. Specific treatment heals them quickly. The consolidation of fractures can give rise to bone calluses (Fig. 25.6) [13]. Rarefied areas in the bone are the results of true gums which may become definitive necrosis. On X-ray they result in clear, rounded areas of variable size,

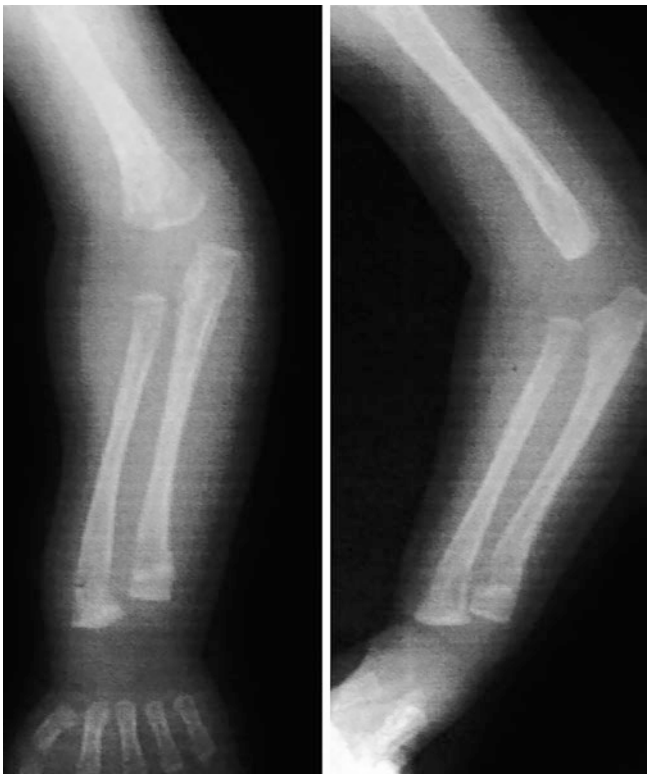

Fig. 25.2 Clear metaphyseal bands, stage 2. (From Benyaich [13], reprinted with permission)

single or multiple, more often at the level of the femoral condyles, at the inner part of the tibial plateau, and at the upper extremity of the ulna. They are often associated with the previously described lesions. In severe forms, exuberant bone neoformations develop at the end of long bones (see Fig. 25.1). Dactylitis is rare. It is more common in the hands than in the feet. In hands, proximal phalanges but also metacarpal bones are characteristically involved. In the feet, dactylitis may occur in the metatarsal bones. It usually realizes a significant thickening of the bone with sclerosis of the cortex [16]. Ultrasound findings of abnormalities plus a positive maternal serology associated with X-ray data will provide sufficient basis for a diagnosis of congenital syphilis [17]. However, because lesions are often asymptomatic, the US CDC recommends systematic serologic screening [18].

Secondary Syphilis

Bone involvement is considered rare in secondary syphilis, the mucocutaneous lesions being the main expression of the disease at this stage. However, syphilitic bone involvement has been reported in 0.15–9.7% of the cases, more often when there are important cutaneous manifestations and systemic involvement [19–21]. However, it often remains unrecognized for a long time even if destructive bone lesions are

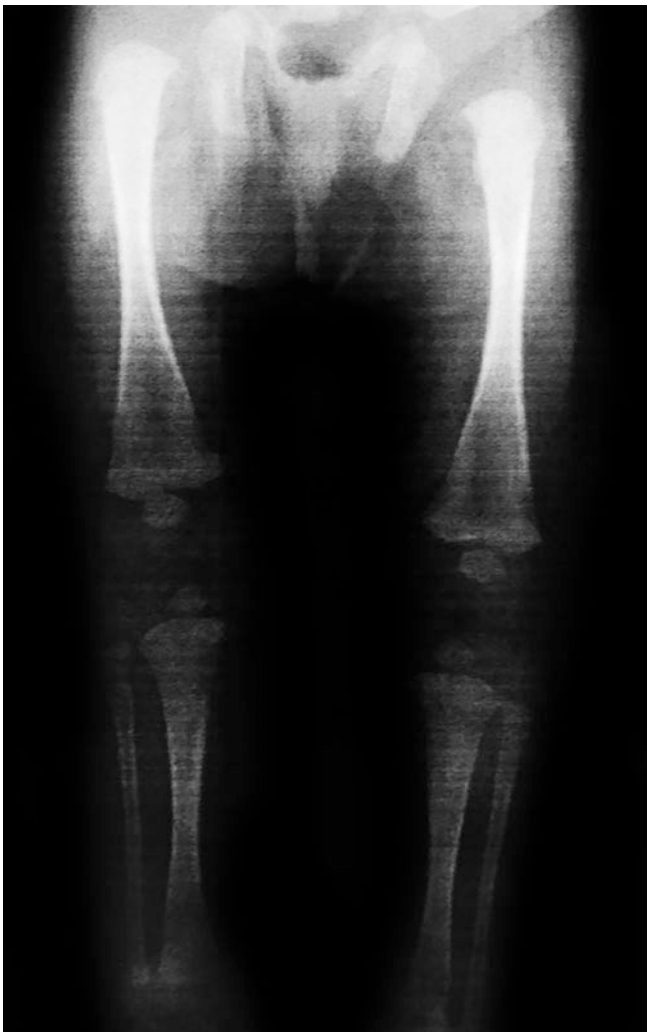

Fig. 25.3 Wimberger's sign: the ossification zone disappears and is replaced by deep symmetrical erosions at the inner edge of tibia metaphysis, stage 3. (From Benyaich [13], reprinted with permission)

increasingly observed thanks to the advance of radiologic technology in recent decades, such as bone scintigraphy, CT scan and MRI [20, 22]. The mechanism of bone involvement is spirochetal invasion of periosteal vascular beds which leads to inflammation and granulation tissue formation, the extension of which into the Haversian canals causes osteitis and osteomyelitis [20]. It mainly involves the skull especially the frontal and parietal bones in patients suffering from headache and infiltrated nodules of the scalp as reported even in recent case reports [22–29]. On conventional radiographies, osteolysis with a "worm-eaten" appearance may be described [22–24] (Fig. 25.7). A solitary lesion of the skull, although rare, has also been reported [26]. In this rare case, it is difficult to distinguish radiologically a syphilitic osteomyelitis from other radiolucent lesions of the skull, such as eosinophilic granuloma, multiple myeloma, or cystic fibrous dysplasia [26]. Kusler et al. recently reported four lesions of

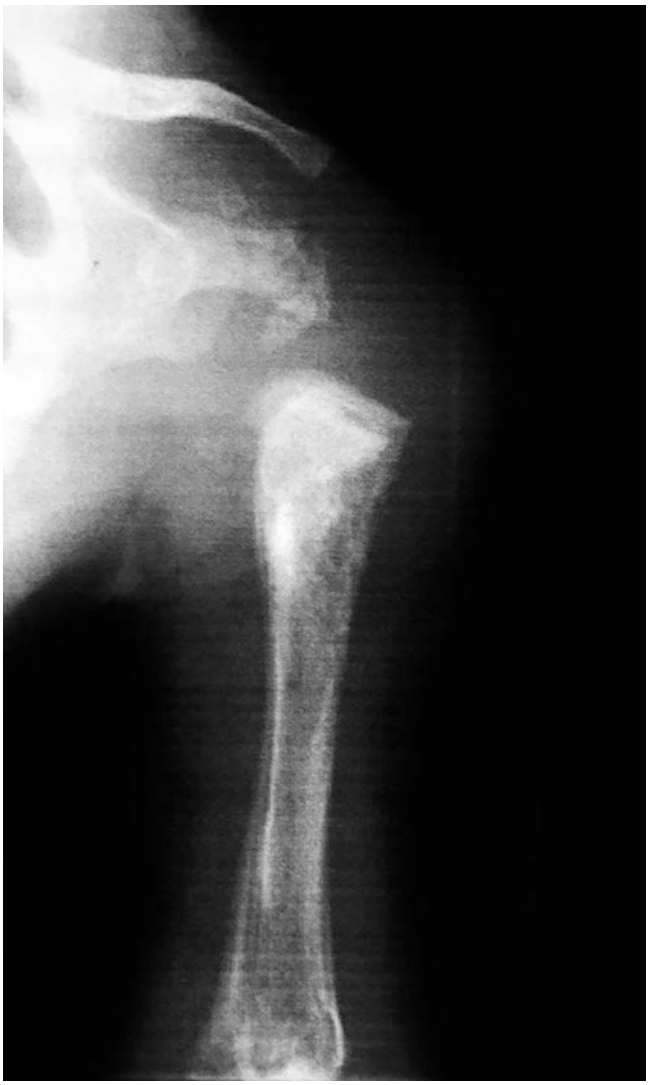

Fig. 25.4 Fracture of the humerus, stage 4. (From Benyaich [13], reprinted with permission)

the skull inside which TP has been found [28]. In all these cases, bone scintigraphy as well as CT and MRI may help demonstrating the site of the lesion, then the marrow space involvement, the periosteal process, and the degree of intracranial expansion [23, 24, 26]. The ribs, the sternum, and the clavicle may also be involved [16, 21]. Involvement of the long bones is rare [21]. Subperiosteal bone neoformation and painful swelling are the results of the syphilitic inflamed periosteum. Pain may be severe, triggered at the slightest pressure and felt as a deep pain. This severity may prevent sleeping. Bone pain may be misdiagnosed as neuropathic pain [30]. It can be accompanied by edema, tenderness and erythema. X-ray shows osteolytic oval lesions with punched out lucencies, with clearly defined or fuzzy outlines. If misdiagnosed, even if rare, osteolytic lesions may be extensive, realizing important bone defects as described in a case reporting the disappearance of the femoral head and neck

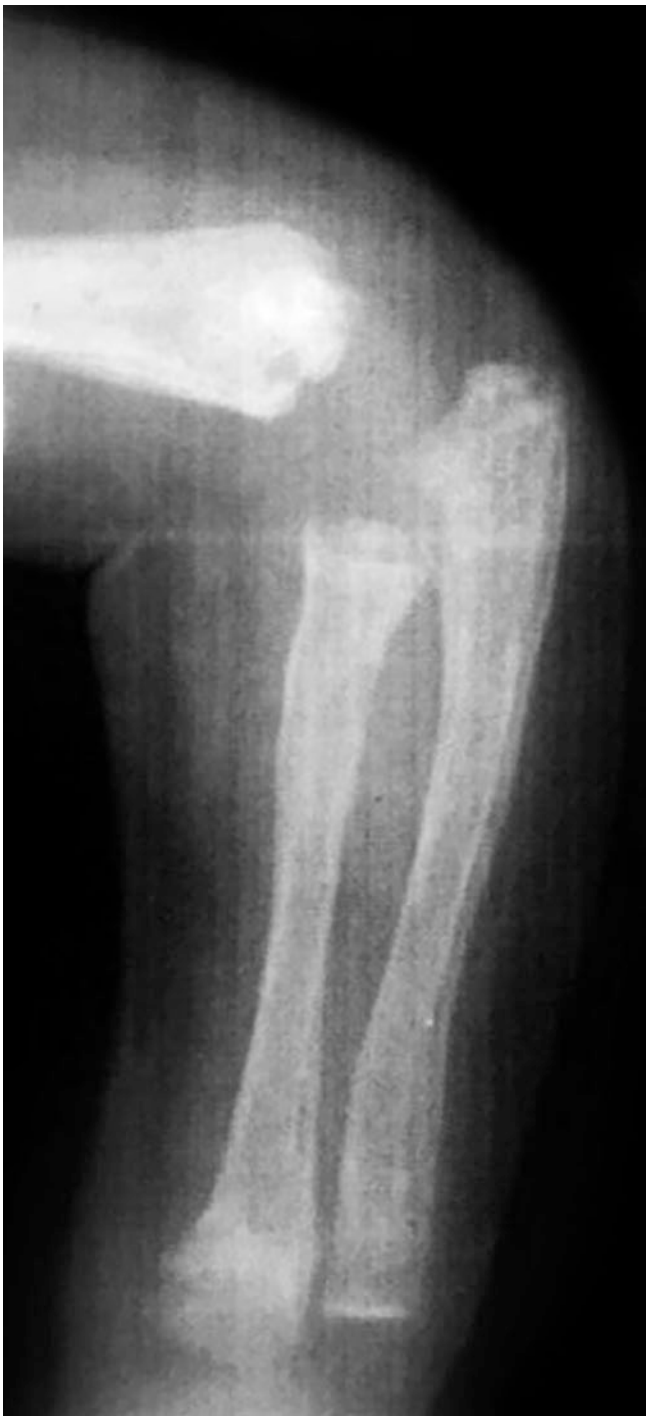

Fig. 25.5 Syphilitic periosteitis. (From Benyaich [13], reprinted with permission)

[31]. More frequently, X-ray shows condensing lesions with periosteal irregular patches, extended to the whole diaphysis. The mixed forms are less frequent and give a blurred appearance to the diaphyses of long bones, mainly the tibia and the fibula.

Arthritis in secondary syphilis is rare, estimated at 4–8% [21]. Arthralgias are more frequent and due to the neighboring

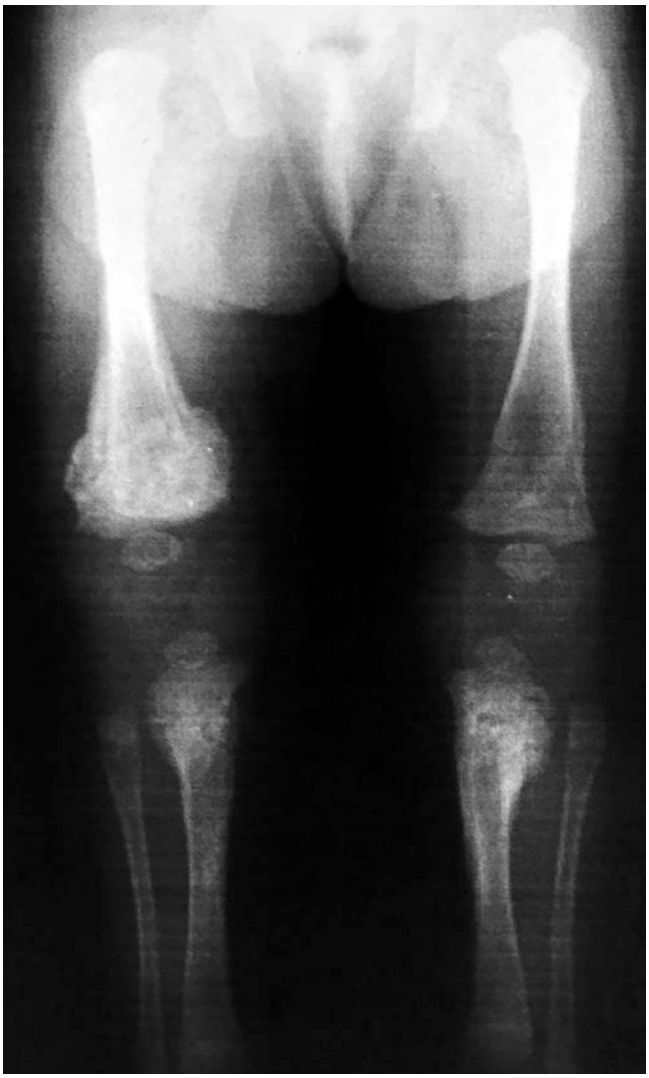

Fig. 25.6 Bone calluses in the right femur and both tibias. (From Benyaich [13], reprinted with permission)

bone involvement. X-rays usually show thickening of the soft parts. Joint involvement may be either monoarthritis [32] or more often polyarthritis. Joint involvement can mimic various rheumatological diseases such as systemic lupus erythematosus, Lyme disease, rheumatoid arthritis, vasculitis, sarcoidosis or lymphoma [21, 33, 34]. In LMICs, syphilis can also mimic rheumatic fever [35]. In some conditions, syphilis may even be associated to systemic diseases, making the differential diagnosis difficult [36]. In addition to the presence of an acute or subacute polyarthritis, attention has to be paid to the pauciarticular, less migratory, preferential involvement of the knee [21]. Low back pain secondary to spondylitis or sacroiliitis is also reported [37]. ESR and CRP are elevated and the joint fluid is usually inflammatory even if not in some reported cases [37]. There is no evidence of the presence of TP in the joint [37] even if there are some recent data about its presence using electron microcopy [21, 38]. The lesions heal under specific treatment. However, sequelae may remain such as sacroiliac osteosclerosis following sacroiliac involvement [39].

Muscle involvement is rarely reported, responsible for myalgia or myositis [40, 41], which can be associated with HIV [42]. Nelson et al. reported a case of rhabdomyolysis and acute renal failure with syphilitic myositis with a favorable outcome after penicillin treatment [43]. Only a few cases of *syphilitic tenosynovitis* are reported, usually associated with joint involvement, best studied by MRI and rapidly resolving with treatment [44–46].

Tertiary Syphilis and Late Congenital Syphilis

Bone lesions of late congenital syphilis occur in children and adolescents between 5 and 20 years of age; in adults, they appear years after the chancre. The tibia as well as the femur and bones of the forearm, the skull and the bones of nasal cavities are most commonly affected. Unlike secondary syphilis, bone involvement is characterized by focused, isolated and asymmetrical lesions [47]. Syphilitic osteitis may produce periosteitis, osteomyelitis, osteitis, and gummatous osteoarthritis. The short bones like the phalanges and the flat bones (skull, bones of the nose) are often involved. Pain in tertiary syphilis is classically described as excruciating, lancinating or constrictive, and nocturnal [47]. In tertiary syphilis and congenital syphilis, spontaneous fracture of the affected bones and fistulization to the skin of a bone gum are rare but not exceptional in LMICs [48].

Tertiary Syphilis Is Remarkable for Hyperostosis The condensing forms on the long bones or the skull produce localized or pandiaphyseal cortical hyperostosis. The subperiosteal neo-formation forms a sheath around the diaphysis and can reach a considerable thickness and hardness. In children, this thickening and the evidence of periosteal reaction tend to become more intense and are responsible for successive layers of new bone laid down under the periosteum realizing the "onion peel periosteum"[16]. This thickening, coupled with healthy bone, may cause a local acceleration of growth leading to the classical "saber blade" deformation with normal fibula [49, 50]. Cortical dedifferentiation is possible in late congenital syphilis, involving the external and superior metaphyseal region of the tibia up to the upper two-thirds of the diaphysis [49, 50].

The osteolytic lesions are less frequent. They result from gummy osteitis. They electively concern the flat bones most often of the skull and the face as well as the palate and the metaphysis of the long bones. They form one or more clearly outlined juxtaposed geodes, often surrounded by a condensed margin, more rarely blowing the adjacent cortex and

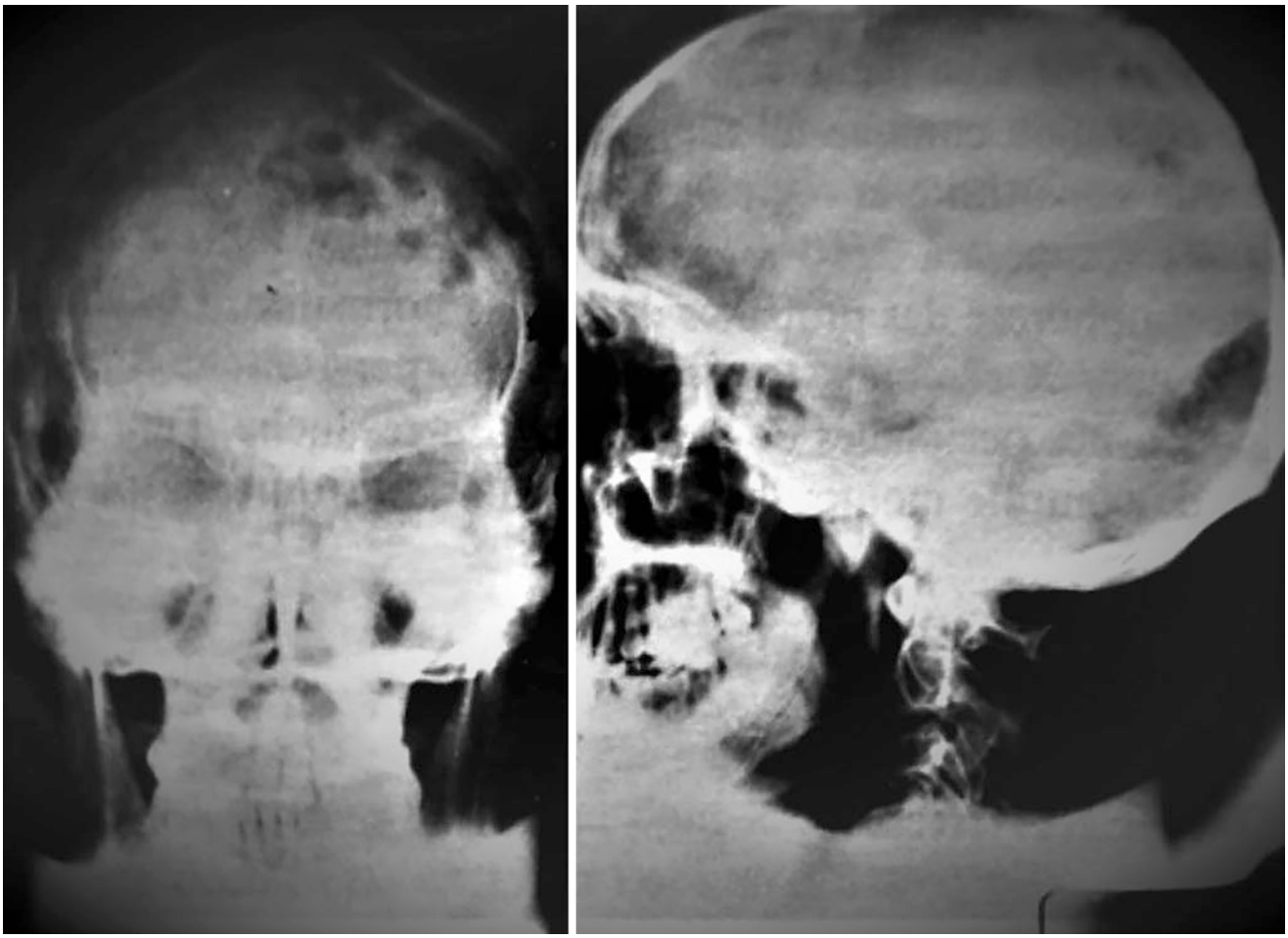

Fig. 25.7 Parieto-occipital lytic areas in a patient presenting a thrombosis of the superior sagittal sinus with syphilitic cranial osteitis. (From El Alaoui et al. [23]. Copyright © 1992, Elsevier Masson SAS. All rights reserved. Reprinted with permission)

containing bony sequestra. When multiple, these lesions may be sometimes coalescing, realizing a real bone lysis.

Mixed condensing and rarefying forms are rare. Hyperostosis prevails at long bones diaphysis whereas rarefaction is more frequent in spongy bone of short bones, metaphysis and epiphysis. In the latter, bone rarefaction, due to gummy osteoperiostitis, is often associated with irregular peripheral hyperostosis. When involved, fingers or toes have a typical spindle shape, and the process may result in deformity and shortening [51]. Syphilitic spondylitis has also the same pattern [51]. When osteocondensation predominates, the bone appears thickened, condensed, and perforated with multiple lacunas.

Joint lesions of tertiary syphilis are rare. They may be either non-tabetic or more significantly tabetic lesions, the neuropathic or so-called Charcot joint being the most characteristic finding [21, 52, 53]. Gummatous involvement of the synovium remains an unusual manifestation.

Non-tabetic joint lesions induce chronic syphilitic synovitis mainly affecting large joints, most often the knees, and are related to joint development of syphilitic gums [21]. In children, Clutton arthropathies induce symmetrical chronic painful synovitis of the large joints, usually knees and elbows. They appear between the age of 8 and 15 years. Joint fluid is usually inflammatory (between 10.000 and 45.000 cells/mm^3), predominantly with lymphocytes [21].

Tabetic arthropathy (TA) was, in the past, the leading cause of neuropathic arthropathy. After the first description of neuropathic arthropathy by Mitchell in 1831, TA was described in detail by Jean Martin Charcot in 1868 [54]. TA due to syphilitic neurological involvement occurs in 5–10% of tabetic patient series [21, 55, 56]. Joint destruction usually occurs at the age of 40–60 years [53]. Sensory and trophic disorders cause osteoarticular dislocations characterized by their rapid and even abrupt onset (a few days or even a few hours), without pain or fever (Fig. 25.8). However, insidious onset is also reported. The mechanism of TA onset remains under debate. Both neurotraumatic and neurovascular mechanisms which complement each other could be

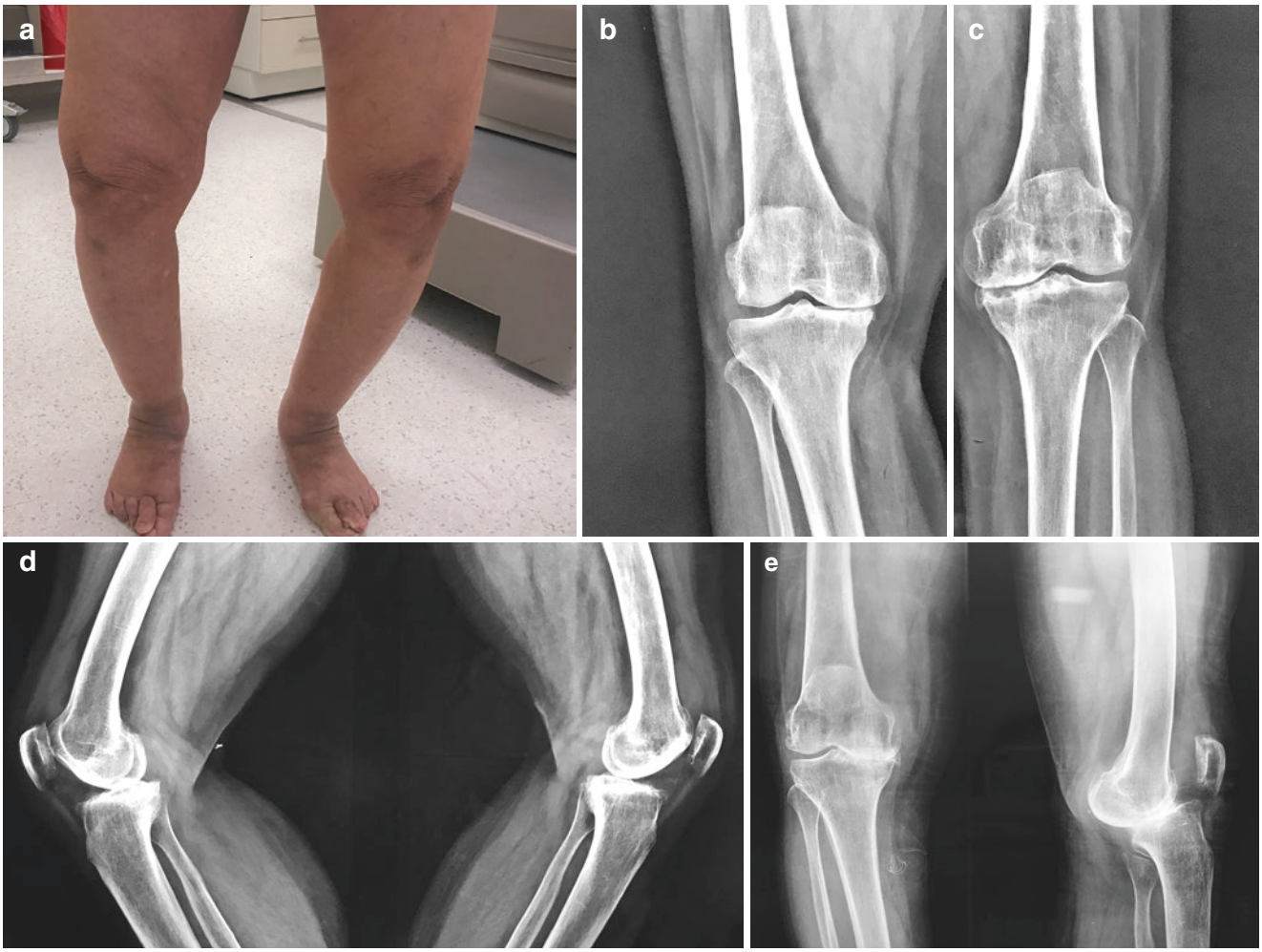

Fig. 25.8 Tabetic arthropathy in a 65-year-old woman. (**a**) Painless knee instability. (**b**) Severe osteoarthritis in both knees. On the right knee, rarefied areas on the tibial plateau, the femoral condyles, and the femoral metaphysis evoking gummy bone involvement. (**c, d**) Onset of a posterior painless luxation of the left femur within 15 days

involved [54]. They localize mainly on the large joints of the lower limbs probably because of the predominant thoracolumbar spinal cord lesions and because of the weight-bearing function of these joints underlining thus the role of trauma. Trauma and microtrauma are considered as significant on these "anesthetized" joints and a traumatic antecedent would be found in about half of the cases [52, 53]. The lesions are closely related to osteoarthritis and combine cartilaginous atrophy, subchondral bone sclerosis and periarticular bone construction (Fig. 25.8). However, it is the intensity of these basic signs and their rapidity of evolution that make the more developed forms of TA so characteristic (Fig. 25.9). However, two main patterns can be described, hypertrophic and atrophic, which can also realize together a mixed pattern. When hypertrophic, the joint involvement can be compared to a prolific osteoarthritis characterized by the predominance of osteophytosis described as bizarre-shaped osteophytes and subchondral osteosclerosis [21, 57]. The joints most often involved are those of the lower limbs, the knee, the ankle, and the feet. The atrophic type is more common in non-weight-bearing joints [54]. It results in osseous resorption, the importance of which is variable. It leads in the most severe cases to the destruction of the epiphysis mainly in the hip and shoulder [58]. Different kinds of mixed presentations (hypertrophic and atrophic) may be described (Fig. 25.10). Progressive absorption of phalanges gives a decrease in bone length and width, resulting in a "pencil sharpening" appearance of the bony ends [59]. Spine involvement leads to hypertrophic development of osteophytosis (Fig. 25.11) sometimes associated with vertebral fractures [54, 60]. A pure destructive lesion may be seen due to gummas in bone which could look like soft, tumor-like lesion [61]. Acute vertebral collapse and cauda equina compression may occur [62]. The association of suspended lesions interposed between healthy areas should assist with the diagnosis.

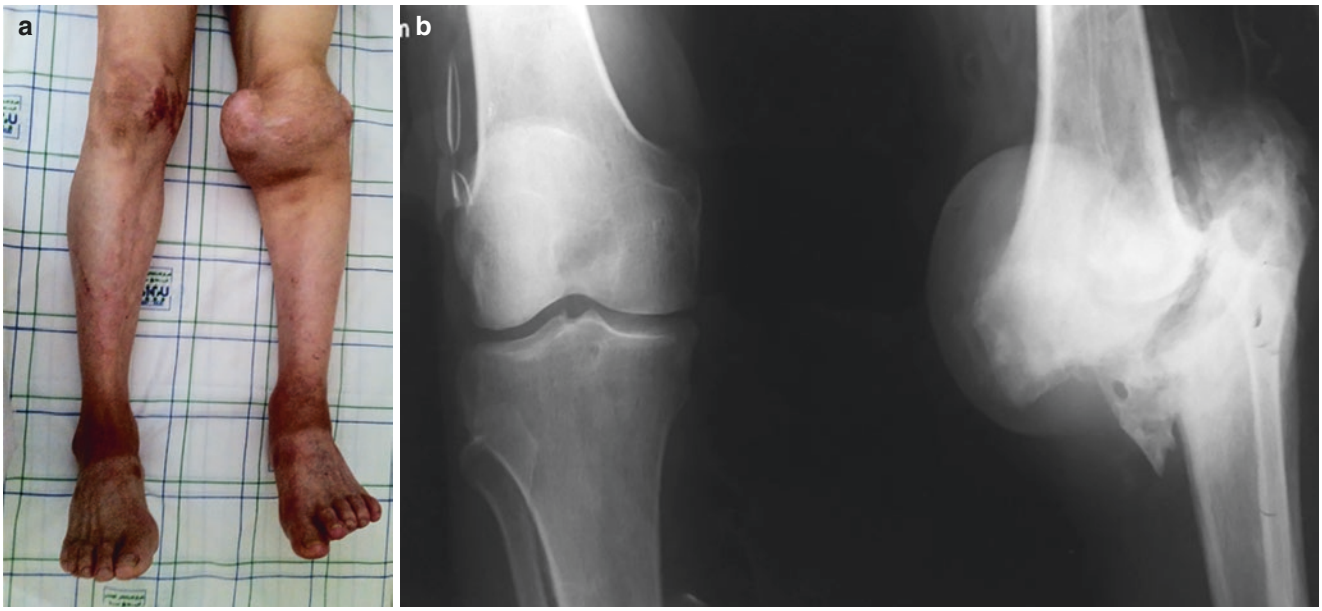

Fig. 25.9 Severe tabetic arthropathy in a 55-year-old man. (**a**) Painless severe deformity of the knee. (**b**) Destruction of the articular surface, dislocation, fracture, debris

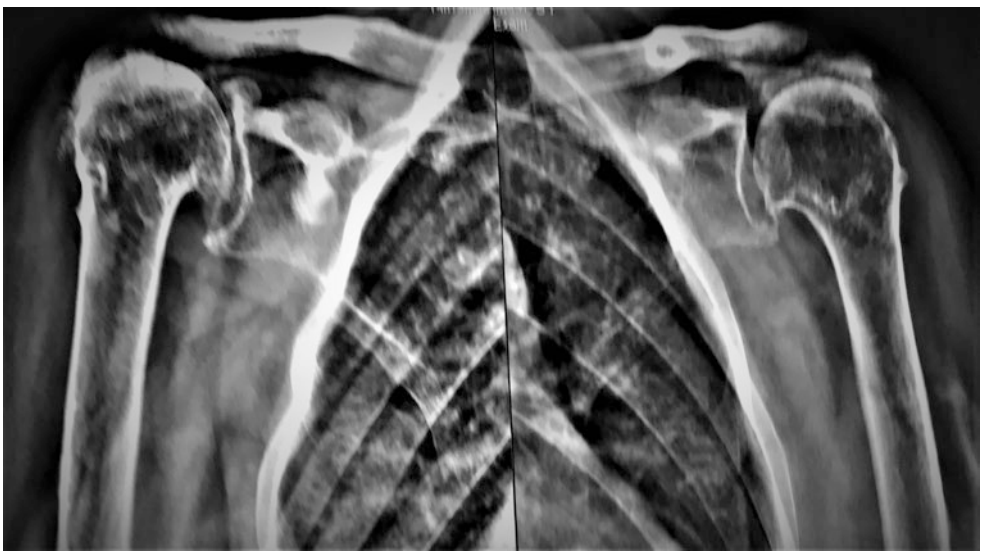

Fig. 25.10 Mixed, hypertrophic and atrophic involvement of the shoulders and the clavicles, osseous debris (patient Fig. 25.8)

Obviously capsuloligamentous and tendinous involvement is also present. The synovium is hypertrophic, sometimes hemorrhagic, and may present areas of cartilaginous and/or osseous metaplasia, explaining the frequent presence of intra-articular foreign bodies. Ligaments are distended and often loosen, contributing to the disorganization and subluxation of the joint.

Joint changes usually precede the neurological deficit. Patients present with a single, bilateral, or even multifocal painless, swollen, and deformed joint [54, 63]. In advanced stages, bone destruction, along with the changes in soft tissues, causes deformities. The movements are of normal or exaggerated amplitude, leading quickly to joint dislocation and to spontaneous fractures. Their slow and incorrect consolidation leads to vicious postures [49]. The overlying skin is often hyperemic. In advanced cases, large osteophytes can be palpable next to the joint, sometimes with subluxation and loose fragments, also described as a "bag of bones" (see Fig. 25.9) [57]. Because trophic lesions are often associated with mechanical factors, patients often suffer from perforating wounds at the points of support, such as the foot [49]. Neurologic examination shows loss of deep pain sensation and proprioception in most patients. In advanced cases, there may be ataxia and a positive Romberg sign. Absent tendon reflexes in the lower limbs and Argyll Robertson pupils are seen in up to 90% of patients with tabes dorsalis and are highly characteristic findings. Moreover, it is remarkable that patients have symptoms that

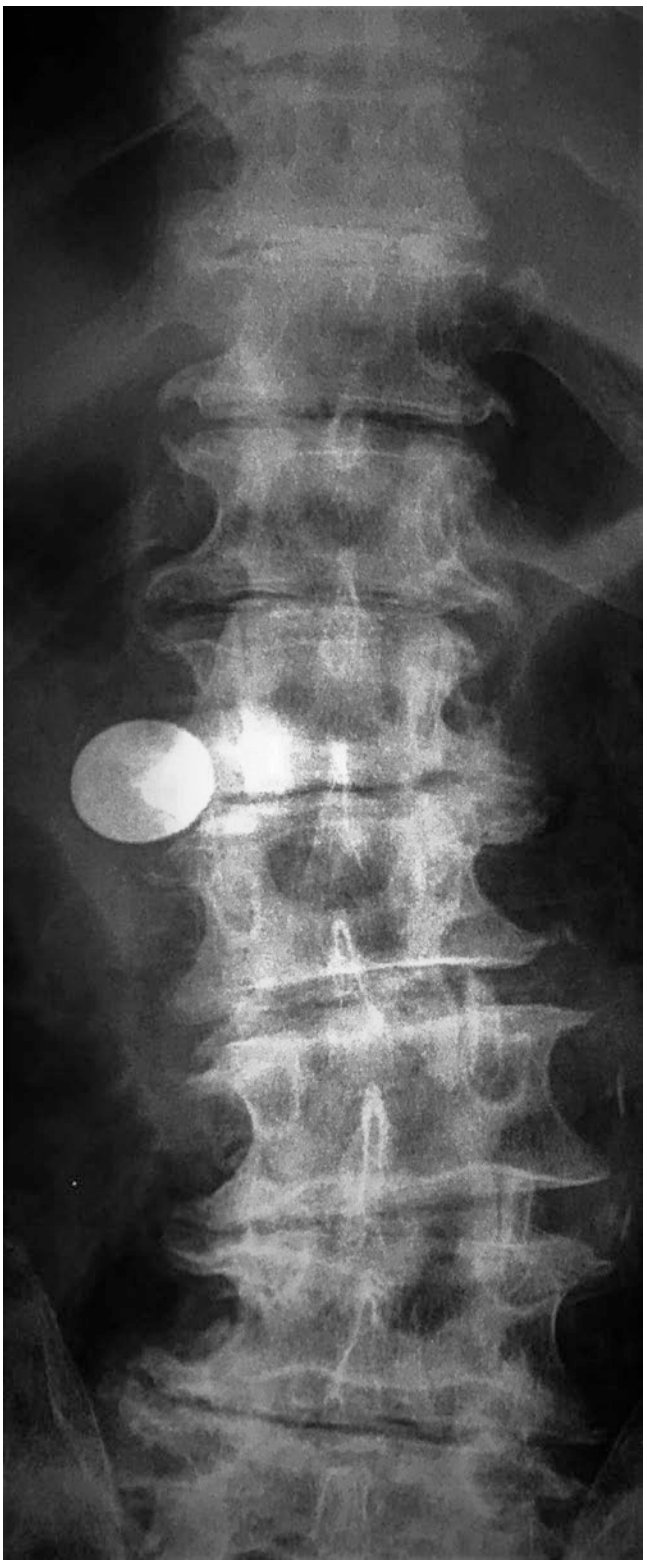

Fig. 25.11 Hypertrophic lumbar spur formation and marked osteosclerosis (Same patient Fig. 25.8)

are much milder than would be expected on the basis of radiological findings. The radiological aspects are the faithful translation of anatomopathological phenomena. As expected from the above description, abnormal findings on radiographs include subchondral sclerosis, osteophytosis, subluxation, and soft tissue swelling. Long-standing neuroarthropathy is characterized by a disorganization of the joint (see Fig. 25.9). These radiographic features are pathognomonic and no further imaging is necessary. However, early changes may resemble infection, osteonecrosis, calcium pyrophosphate dihydrate crystal deposition disease, psoriatic arthritis, osteoarthritis, and osteolysis with detritic synovitis [58]. Bone scintigraphy typically demonstrates increased radiotracer uptake in the regions of skeletal abnormality caused by syphilis. MRI and radioisotope scan can help in differential diagnoses [64]. Tabetic arthropathies may be complicated by joint chondrocalcinosis [21, 53, 65]. A pathogenetic synergism of the two conditions is postulated. Calcium pyrophosphate microcrystals could act as traumatic factors. Moreover, because joint destruction may be seen in both conditions, neuroarthropathy should be excluded before proceeding with endoprosthetic joint replacement [65].

Clinical stigmas may also develop at this stage, either because infection occurred at a critical growth stage or as a direct result of the disease [8, 21, 49, 50]. Stigmas related to infection during a growth phase include "saddle nose," due to the enlargement of the distal part of the nose realizing a kind of depressed bridge or "saber" shin with anterior convexity found in the tibia and/or the bones of the forearm. They also include poorly developed and/or enameled, notched, peg-shaped incisors (Hutchinson teeth) or malformed molars (Fournier teeth) [49, 50]. Short maxilla, arched palate, protruding mandible and scaphoid scapula are also reported. Periosteitis may be responsible for the frontal hump of Parrot, the parasternal clavicular enlargement, and thickening of Higoumenakis. The mucous gums may cause palatal perforation.

Muscle and articular structure involvement have become rare. However, muscle weakness may result from spinal cord or root involvement, the progressive degeneration of which may result in severe amyotrophy of the lower limbs and of the hand [41, 66–68]. Syphilitic bursitis may be gummy bursitis extending from the neighboring tissue to the bursa or originating in the bursa itself, rapidly resolving after penicillin therapy [69].

Treatment

The mainstay of syphilis treatment is parenteral penicillin, whatever the stage of the disease, despite the relatively modest clinical trial data that support its use. TP remains extremely susceptible to penicillin, an antimicrobial agent targeting bacterial cell wall synthesis [70].

Infected infants born to mothers who did not receive proper treatment and prevention and who are not able to be monitored for a long time after birth should be treated at birth [8]. CSF should be examined before treatment. If the

CSF is normal, a single intramuscular injection of 50.000 units/ kg up to 2.4 million units (MU) of benzathine penicillin G is used. If the CSF is abnormal, it is necessary to use aqueous penicillin G at the dose of 50.000 units/kg given intramuscularly or intravenously twice daily for a minimum of 10 days. Alternatively, a single daily intramuscular injection of 50.000 units/kg of procaine penicillin may be given for 10 days.

In early syphilis (primary, secondary, or early latent), the treatment is based on a single intramuscular injection of 2.4 MU of benzathine benzylpenicillin. The alternative, in case of allergy, is doxycycline 200 mg/day (simultaneously active against other STD) or erythromycin 2 g/day for 15 days [71]. In the case of late syphilis (tertiary, latent late), the role of treponemal proliferation is secondary to tissue reactions, even if TP remains present in the body. This explains that the tissue lesions are practically insensitive to antibiotherapy [70]. However it is recommended in order to sterilize the lesions to use three intramuscular injections at 1 week apart of benzathine benzylpenicillin 2.4 MU and in the case of allergy, doxycycline 200 mg/d or erythromycin 2 g/day for 28 days [72]. In the case of associated neurosyphilis, the treatment is then based on penicillin G, 18–24 MU/d in six infusions for 14–21 days. Joint effusions, joint lavage, local corticotherapy, or synoviorthesis may be used even if their results remain poor [53]. Because of the role of trauma, whatever their intensity, in the worsening of the impairment, palliative reduction of instability by immobilization and and/or diverse ways of contention is important [53]. Surgery may be discussed in the most impaired forms of TA. Attempted joint prostheses have often resulted in their loosening, even if fair results have also been reported [73, 74]. Up to 60% of patients with early syphilis and a significant proportion of patients with later stages of syphilis may experience, in the few hours after therapy administration, a transient febrile reaction known as Jarisch-Herxheimer reaction. It is not appropriate to reduce the doses, as this does not prevent the reaction [70]. Its pathogenesis is unclear, but it may be caused by the liberation of antigens from spirochetes. It usually disappears within 12–24 hours of therapy. Even if salicylates may be effective, corticosteroids have been used to prevent the Jarisch-Herxheimer reaction.

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Lyme Disease and Arthritis

26

Zuhal Arzomand, Matthew White,
and Anthony M. Reginato

Overview and Pathogenesis

Summary

- Lyme disease is caused by *Borrelia*—a group of pathogenic bacteria (spirochetes) and is transmitted by soft or hard ticks [1, 2].
- *B. burgdorferi*, found in the United States, is carried by the hard tick *I. scapularis* (Fig. 26.1), which can also harbor other bacterial and viral species, resulting in coinfections [3].
- Commonly seen as a feature of late stage infection, Lyme arthritis is accompanied by intense innate and adaptive immune responses [4].

More than 30 years ago, *Borrelia burgdorferi sensu stricto* was identified as the pathogenic organism that causes Lyme disease when 51 patients from rural Connecticut were found to have a systemic illness with subsequent arthritis. *B. burgdorferi* sensu lato complex is a diverse group of bacteria that includes more than 20 spirochete species [5, 6].

The enzootic cycle of *B. burgdorferi* is complex. *Ixodes* ticks have a two-stage life cycle and require one blood meal per stage of development, from larva to nymph to adult (Fig. 26.1). All stages of *I. scapularis* are involved in the transmission of *B. burgdorferi* to mammals. Adult *I. scapularis* ticks predominantly feed on deer, which are incompetent hosts for *B. burgdorferi* but gave rise to the name "deer tick" (Fig. 26.2). Transmission to humans typically occurs during the nymph phase of the tick's life cycle, although all three phases can feed on humans [5].

Once transmitted through injection into the skin, *B. burgdorferi* can spread throughout the body and has been identified histologically in a diverse array of tissues, including heart, skin, eyes, central nervous system, and joints [7]. *B. burgdorferi* strains have been recognized to disseminate to joints, tendons, and bursa early in the infection and can be asymptomatic or lead to migratory arthralgias. The clinical manifestations of Lyme disease result from active systemic infection by *B. burgdorferi* as well as the immune response to the presence of the spirochete in body tissues [4].

Commonly seen as a feature of late stage infection, Lyme arthritis is accompanied by intense innate and adaptive immune responses. Pathogen-specific, genetic, and immune-mediated factors are responsible for antibiotic-refractory Lyme arthritis in which articular symptoms persist despite appropriate treatment. The highly inflammatory *B. burgdorferi* RST1 strains can cause chronic joint inflammation and contribute to the development of antibiotic resistance [4]. The concept of molecular mimicry leading to a reactive type of arthritis as an explanation for antibiotic-refractory Lyme arthritis was suggested several years ago. Enhanced Th1 activation triggered by the binding of HLADR alleles to the outer-surface protein A (OspA) of *B. burgdorferi* contributes to the excessive inflammation in chronic Lyme arthritis. Interestingly, uncontrolled immune responses have been linked to a TLR1 polymorphism (1805GG), which is seen in many European Caucasians. Synovial fluid of patients with antibiotic-resistant arthritis has been shown to be deficient in a specific regulatory T-cell (FoxP3+), which has been hypothesized to play a key role in counteracting excessive articular inflammation. Disruption of immune system homeostasis triggered by *B. burgdorferi* leads to infection-induced autoimmunity against endothelial cell growth factor (ECGF), ultimately damaging the synovial microvasculature

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_26

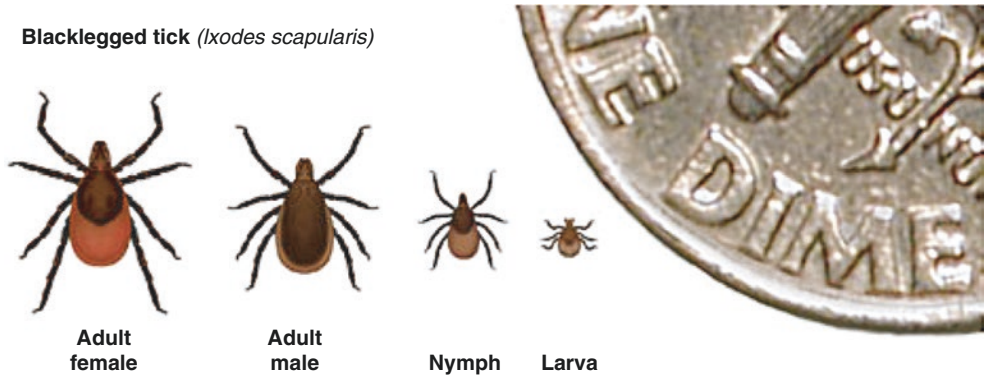

Fig. 26.1 Stages of blacklegged tick *Ixodes scapularis* (from right to left: larval stage, nymphal stage, adult male, adult female. Adult ticks are approximately the size of a sesame seed, and nymphal ticks are approximately the size of a poppy seed. (From: Centers for Disease Control and Prevention (CDC). Transmission - Lyme Disease [Internet]. Cdc.gov.2018 [cited 22 October 2018]. Available from https://www.cdc.gov/lyme/transmission/blacklegged.html)

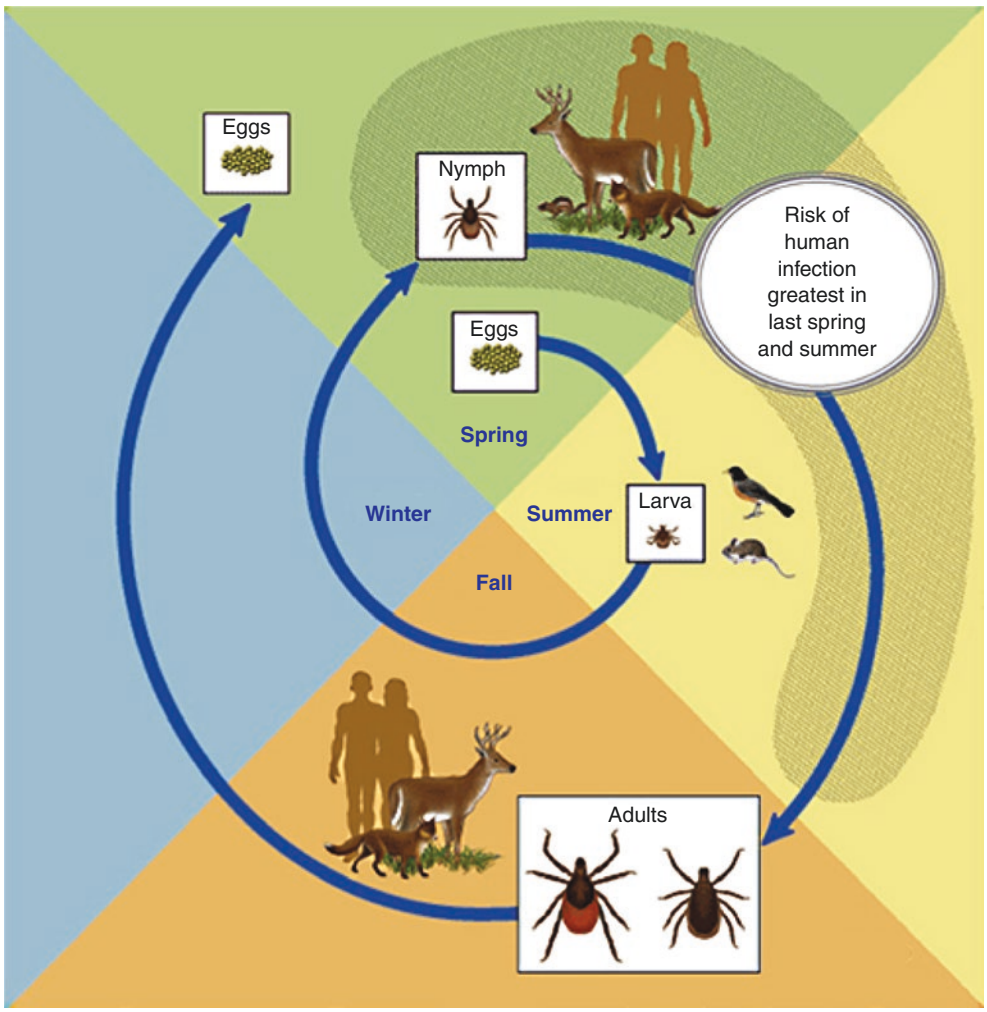

Fig. 26.2 Life cycle of blacklegged ticks (Ixodes scapularis) that can transmit Lyme disease. They can feed from mammals, birds, reptiles, and amphibians. The ticks need to have a new host at each stage of their life. (From: Centers for Disease Control and Prevention (CDC). Transmission - Lyme Disease [Internet]. Cdc.gov.2018 [cited 22 October 2018]. Available from https://www.cdc.gov/lyme/transmission/blacklegged.html)

[4]. With the assistance of antibiotics and in rare cases immunosuppressive therapies, the innate and adaptive immune systems eventually regain homeostasis and arthritic symptoms resolve [4].

Epidemiology

Summary

- In 2016, approximately 26,203 cases of Lyme disease were confirmed in the United States [8–10].
- Transmission occurs most frequently between late May and late September.
- In 2015, 95% of all cases in the United States were reported from the northeastern, north central, and mid-Atlantic states [11].
- Most *Borrelia burgdorferi* infections occur in two specific age groups: 5–15 years and 45–55 years of age [12].

Lyme disease is the most commonly reported vector-borne infection in the United States. In 2016, the US Centers for Disease Control and Prevention reported 26,203 cases of confirmed Lyme disease and 10,226 probable cases (Fig. 26.3) [8–14]. Endemic regions include the northeastern/mid-Atlantic states, the north central states, and some states along the Pacific coast (Fig. 26.4) [15]. Lyme disease has a high frequency in central Europe and Scandinavia and also occurs in Russia, China, and Japan [13]. Lyme disease transmission occurs most frequently from late spring through fall, as the *Ixodes* nymphs mature, with peaks in June and July [10]. The majority of *Borrelia burgdorferi* infections occur in two specific age groups: 5–15 years and 45–55 years of age [12].

After an outbreak of monoarticular and oligoarticular arthritis in children located in Lyme, Connecticut, during the 1970s Lyme arthritis became recognized as an entity of Lyme disease, a complex multisystem illness. Before the initiation of antibiotic treatment, approximately 60% of untreated patients developed Lyme arthritis [4].

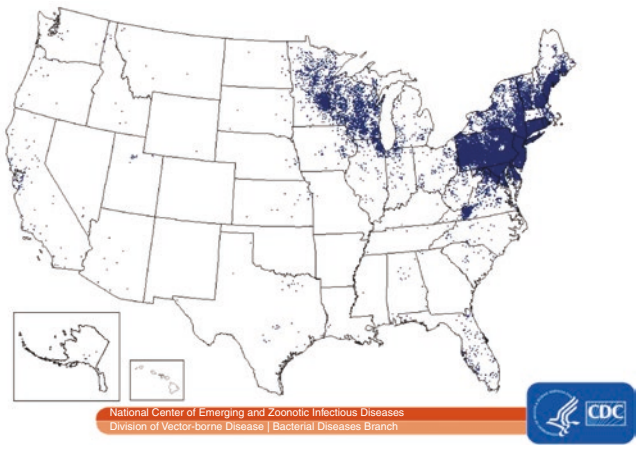

Fig. 26.4 Reported cases of Lyme disease in the United States in 2016. Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. People travel between states, and the place of residence is sometimes different from the place where the patient became infected. (From Centers for Disease Control and Prevention [15]. Available from https://www.cdc.gov/lyme/resources/reportedcasesoflymedisease_2016.pdf)

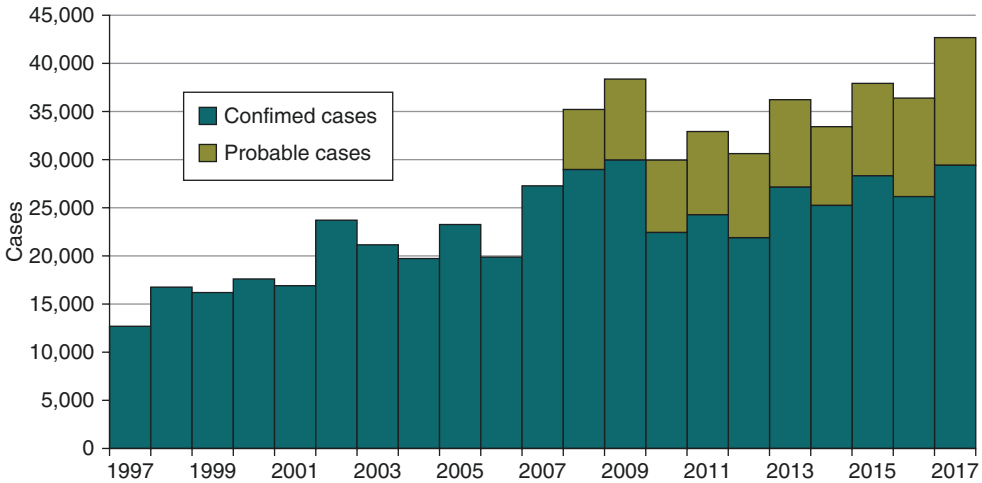

Fig. 26.3 Lyme disease—Reported cases by year, United States, 1997–2017. (From Centers for Disease Control and Prevention [14]. Available from: https://www.cdc.gov/lyme/stats/graphs.html)

Clinical Phases

Summary

- There are three phases of Lyme disease: early-localized, early-disseminated, and late disease (Table 26.1) [16, 17].
- To infect a host, the tick must remain attached to the host for 24–48 hours [18].
- Infections can be prevented by removing the tick within 24 hours of attachment [19].

Classically, infection by *Borrelia burgdorferi* leads to a well-described sequence of clinical symptoms that can be divided into three distinct phases: early-localized Lyme disease, early-disseminated Lyme disease, and late Lyme disease. A fourth phase, termed chronic Lyme syndrome, is a controversial entity that has been discredited as representative of refractory infection; however, the possibility that it is a persistent immune-mediated reaction cannot be fully excluded (Table 26.1) [16, 17, 20, 21]. Transmission to a host by *Ixodes scapularis* requires the tick to be attached to the host for 24–48 hours of feeding; transmission rates are higher if the tick is attached for more than 48 hours [20].

Table 26.1 Clinical manifestations of Lyme disease

Manifestation	Approximate prevalence in untreated patients (%)	Associated symptoms
Early-localized disease (occurs days to 1 mo after tick bite)[a]		
EM	80	Fatigue Malaise Lethargy Mild headache Mild neck stiffness Arthralgias Regional lymphadenopathy
Early-disseminated disease[b] (occurs wks to mos after tick bite[a, c])		
Carditis	<5	AV nodal block Mild cardiomyopathy or myopericarditis
Neurologic disease	15	Lymphocytic meningitis Cranial neuropathy (facial palsy-bilateral) Peripheral neuropathy Myelitis or encephalitis (rare)
Musculoskeletal	60[d]	Migratory arthritis
Skin	Not established	Multiple EM lesions Borrelia lymphocytoma (Europe)
Lymphadenopathy	Not established	Localized or generalized
Eye	Not established	Conjunctivitis Iritis Choroiditis Vitreitis Retinitis
Liver disease	Not established	Liver function abnormalities Hepatitis
Kidney disease	Not established	Microhematuria Asymptomatic proteinuria
Late Lyme disease[b] (occurs mos to yrs after tick bite[a])		
Musculoskeletal intermittent	60	Intermittent monoarticular or oligo-articular arthritis
Musculoskeletal persistent	10	Persistent monoarticular arthritis usually affecting the knee
Neurologic	Not established	Neuropathy or encephalitis
Skin	Not established	Acrodermatitis chronica migrans Morphea/localized scleroderma-like lesions (described in Europe)

Data from [16, 20]
AV atrioventricular, *EM* erythema migrans
[a]Only 25% of patients with EM recall a tick bite
[b]Can occur in the absence of any features of Lyme disease
[c]Multiple EM lesions can occur days to weeks following infection with Lyme disease
[d]Incidence following treated EM is unknown but very low

Patients can present initially with any of the three phases of the disease. In a case series, 89% of patients with diagnosed Lyme disease presented with EM lesions, 5% had arthritis, 3% had early neurologic disease, 2% had borrelial lymphocytoma, and 1% had acrodermatitis chronica atrophicans [22]. It is important for providers practicing in regions endemic for Lyme disease to be familiar with these varying presenting symptoms to maximize the utility of diagnostic testing and minimize unnecessary testing and antibiotic therapy.

Early Localized

Summary

- EM lesions, which often appear as a rash with a bull's-eye center, are the most common manifestation of early-localized Lyme disease (Fig. 26.5) [23, 24].
- A diagnosis of Lyme disease can be made based on EM in the absence of positive serology [23].
- Other symptoms in this phase include malaise, fatigue, headache, fever, and lymphadenopathy [25].

Erythema migrans is the most common clinical manifestation of *Borrelia burgdorferi* infection and is the only symptom that is diagnostic of Lyme disease in the absence of serologic confirmation [23]. EM lesions can appear anywhere on the skin (Fig. 26.5) after an incubation period of 3–30 days and are a result of local skin infection by the spirochetes from an infected tick [24–29].

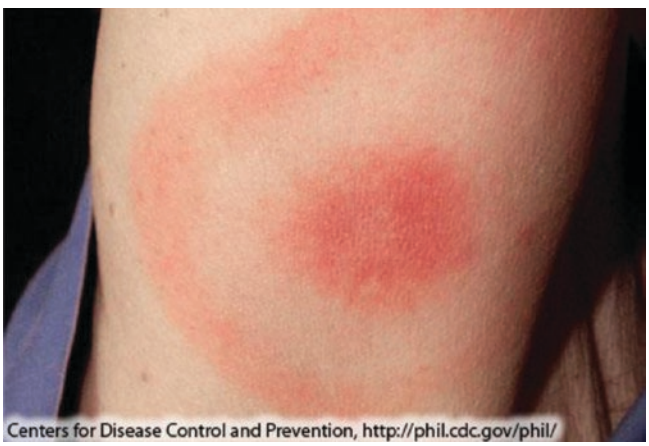

Fig. 26.5 Erythema migrans: "classic" Lyme disease rash. Circular red rash with central clearing that slowly expands. (From Centers for Disease Control and Prevention, http://phil.cdc.gov/phil [29]. Available from https://www.cdc.gov/lyme/images/rashes/CDC_EM.jpg)

Although EM lesions are a classic symptom of Lyme disease, they are not always present or may not be observed in 20–50% of patients [13, 30]. Classic EM is usually a uniform erythematous oval to circular rash, with a diameter of 5–20 cm and a classic bull's-eye center in some cases (19%) [24, 31]. It is often found around the knees, axilla, or in the groin [13, 32–34]. Primary EM lesions are usually painless, although mild pruritus, mild tenderness, or paresthesia may be observed. The differential diagnosis for EM includes insect bites, cellulitis, tinea, and contact dermatitis [13]. Patients may also have systemic signs of infection during the early-localized phase of Lyme disease such as malaise, fatigue, headache, fever, and lymphadenopathy [25]. The lone star tick, *Amblyomma americanum*, is also known to cause a similar EM-like rash and causes a condition called southern tick-associated rash illness (STARI). STARI has been associated with febrile illness accompanied by leukopenia and thrombocytopenia. It is unknown whether patients with STARI would benefit from antibiotics but given similarities in presentation it is often treated with the same antibiotics as Lyme disease [35].

Early Disseminated

Summary

- Rheumatologic manifestations are common in the early-disseminated phase of Lyme disease.
  - Inflammatory arthritis includes involvement of multiple joints with swelling, pain, and synovitis accompanied by fatigue [36].
- Other manifestations include cardiovascular symptoms such as AV conduction deficit, ocular involvement (uveitis, conjunctivitis), and neurologic symptoms (facial nerve palsy, radiculoneuritis, encephalitis) [13, 27, 32, 38–40].

If left untreated, the lymphatic or hematogenous spread of *Borrelia burgdorferi* evolves into early-disseminated Lyme disease. In this phase of infection, patients may have secondary annular skin lesions, diffuse arthralgias or arthritis, generalized lymphadenopathy, carditis, or central nervous system infection. Constitutional symptoms such as headache, malaise, fever, and chills may extend to this phase of infection. Frequently, concurrent symptoms affecting several organ systems are present in the same patient. Secondary or multiple EM lesions may develop due to hematogenous spread of spirochetes.

Rheumatologic manifestations are common in this phase of disease. Lyme arthritis typically affects one or a few large joints, most commonly the knee, and can manifest with large effusions [4]. Arthritis affecting several joints with intense synovitis in a migratory or intermittent pattern is typical at day 1 to 8 weeks after the onset of the rash [36]. Non-specific myalgias and arthralgias may also occur [25]. In these patients, active synovial inflammation is demonstrated by synovial hypertrophy, vascular proliferation, and mononuclear cell infiltration [26, 37]. Inflammatory arthritis due to Lyme disease is accompanied by fatigue and is remitting and relapsing in nature; therefore, the disease may recede before presentation to healthcare providers. This remitting-relapsing course with the absence of fever and general lack of significant pain with movement can distinguish this type of arthritis from septic arthritis [4].

If left untreated, Lyme disease can affect the cardiovascular system. In the United States, approximately 4–10% of patients develop carditis, whereas in Europe the incidence is much lower at 0.3–4.0% [32, 33, 41, 42]. Cardiovascular involvement typically manifests as acute onset of atrioventricular (AV) conduction deficit [13, 32]. Pericarditis and myocarditis may be present; however, dilated cardiomyopathy is uncommon in North America. Left ventricular dysfunction can be present occasionally [13, 32, 38]. Clinical symptoms of carditis may include chest pain, dyspnea on exertion, fatigue, or syncope [24]. AV conduction defects usually resolve in days to weeks after treatment.

Ocular manifestations of Lyme disease have been described, but the spirochete *B. burgdorferi* is not typically isolated in these cases. Uveitis, keratitis, episcleritis, follicular conjunctivitis, retinal hemorrhage or detachment, and optic neuritis may occur at a frequency of less than 5% [38, 39, 43].

Acute neurologic symptoms at this stage of disease include cranial neuropathy of which isolated or bilateral facial nerve palsy is the most common neurologic manifestation. Neuroborreliosis is suspected in patients who present with recent or concurrent EM lesions and serologic findings consistent with recent infection. Meningitis, radiculoneuritis, encephalitis, and myelitis due to *B. burgdorferi* are known manifestations of acute neuroborreliosis. Cerebrospinal fluid analysis reveals a lymphocyte-predominant pleocytosis in cases of central nervous system Lyme infection and intrathecal synthesis of total immunoglobulin (Ig) M, IgG, or IgA. Cerebrospinal fluid examination for spirochetes using polymerase chain reaction assay is not required for diagnosis, although it may be helpful in supporting a diagnosis or in research applications [27, 40].

Late

Summary

- Lyme arthritis is the most common symptom in late Lyme disease and occurs in 60% of untreated patients [25, 44, 45].
- Diagnosis of Lyme arthritis is made after excluding other causes of recurrent or persistent mono- or oligoarthritis, with confirmatory testing by positive IgG immunoblot assay [46].
- Skin symptoms in this stage include acrodermatitis chronica atrophicans and borrelial lymphocytoma [47].

The most commonly encountered manifestation of late Lyme disease is Lyme arthritis, which occurs in patients in whom early manifestations were not recognized and therefore were untreated. Lyme arthritis occurs in 60% of untreated patients with documented erythema migrans. Furthermore, in approximately 10% of patients, the initial *Borrelia burgdorferi* infection is asymptomatic and arthritis may be the first clinical presentation [25, 44, 45]. Joint involvement of Lyme disease in this phase includes recurrent or persistent synovitis of a large joint, most commonly the knee, although oligoarthritis can occur as well [25, 45]. The diagnosis of Lyme arthritis requires a positive *B. burgdorferi* IgG immunoblot assay; however, it is a diagnosis of exclusion and evaluation for other causes of mono- and oligoarthritis should be sought [6, 46]. Synovial fluid analysis is non-specific and reflects the inflammatory nature of Lyme arthritis, with average white blood cell (WBC) counts between 10,000 and 25,000 cells/mm^3 [4, 46]. Although rare, there have been reports of synovial WBC counts as low as 500 cells/mm^3 and as high as 100,000 cells/mm^3. Detection of *B. burgdorferi* by synovial fluid polymerase chain reaction (PCR) assay may help confirm Lyme arthritis, but it is not required for diagnosis and has not been standardized for clinical use. A positive PCR is found in 40–96% of patients prior to antibiotic therapy, the majority of whom will become PCR negative after treatment. However, few patients will remain PCR positive despite treatment with clinical resolution of inflammatory arthritis [4].

Cutaneous findings in late Lyme borreliosis include acrodermatitis chronica atrophicans whereas borrelial lymphocytoma is considered a subacute lesion. Chronic fibrosing skin lesions with bluish discoloration of the skin and epidermal atrophy characterize acrodermatitis chronica atrophicans.

Borrelial lymphocytoma is a painless bluish-red nodule or plaque, usually located on the ear, nipple, or scrotum. PCR assay or direct culture of these lesions may show positive results for borreliosis. Both borrelial lymphocytoma and acrodermatitis chronica atrophicans are usually caused by *B. garinii* and *B. afzelii* and, therefore, are not usually seen in the United States [47].

Neurologic manifestations of late Lyme disease are rare. Subtle encephalopathy, peripheral neuropathy, or encephalomyelitis has been reported as symptoms of late neuroborreliosis [24, 48]. For the diagnosis of encephalomyelitis, objective findings from neurologic examination, cerebrospinal fluid lymphocytosis, and magnetic resonance imaging indications must be present [44]. Patients with chronic symptoms of encephalopathy, axonal polyneuropathy, and encephalomyelitis have been shown to respond to antibiotic therapy [40].

Chronic

Summary

- Experts do not support the use of the term "chronic Lyme disease".
- Vague symptoms that persist after diagnosis and treatment of Lyme disease may fall under the category of posttreatment Lyme disease syndrome (PTLDS).

Experts do not support the use of the term "chronic Lyme disease" as it has been misused to describe people with illnesses unrelated to *B. burgdorferi*. The idea that patients can have late manifestations of Lyme disease without serologic evidence of Lyme exposure has been found to be false [49, 50]. This applies even to patients treated with antibiotics during the perceived acute phase, which is felt to hamper host humoral response to *Borrelia burgdorferi* [44]. In fact, patients who show no symptoms of disease have a very low probability of developing the disease, and serologic testing for these patients is not recommended [51].

There are patients who have been exposed to and fully treated for Lyme disease, who report persistent non-specific symptoms after treatment. This is referred to as posttreatment Lyme disease syndrome (PTLDS) and is hypothesized to have an autoimmune basis [52]. The Infectious Diseases Society of America (IDSA) criteria for PTLDS include a history of treated Lyme disease with resolution followed by fatigue, diffuse musculoskeletal pain, or cognitive impairment not due to fibromyalgia or chronic fatigue syndrome. Prospective studies have shown that this clinical entity has a prevalence of 0.5–13.1%. Symptoms must occur within 6 months of the diagnosis of Lyme disease and persist for 6 months after therapy [23]. PTLDS is a diagnosis of exclusion; therefore, ruling out coinfections with other vector-borne pathogens is important [33, 53, 54]. There is no evidence to support the use of repeat antibiotic therapy for PTLDS, as demonstrated in a large randomized control trial evaluating 280 patients in Europe [55].

Coinfection with Other Vector-Borne Pathogens

Summary

- *Anaplasma* and *Babesia microti* are two common coinfections that can occur with *B. burgdorferi* and should be considered in patients who present after a tick bite with symptoms atypical of Lyme disease [56–58].
- Human granulocytic anaplasmosis (HGA) and babesiosis can be diagnosed by intragranulocytic inclusions and parasites in the blood smear, respectively [23, 59–61].

Ixodes scapularis can serve as a competent host for other pathogenic organisms such as *Borrelia miyamotoi, Anaplasma, Babesia microti,* and tick-born encephalitis virus [56–58]. Clinical signs and symptoms of these infections differ from those of Lyme disease. In patients who present with fever after a tick bite within 1 month of initial exposure, diagnosis and treatment for human granulocytic anaplasmosis (HGA) and babesiosis should be considered. This is particularly true if the patient has a high-grade fever despite appropriate therapy against *B. burgdorferi* or unexplained leukopenia, thrombocytopenia, elevated liver enzymes, or hemolytic anemia, especially in asplenic patients. Treatment of Lyme disease with [drug: doxycycline] has the added advantage of being effective against both *B. miyamotoi* and HGA, but it is not useful for babesiosis [23, 59–61].

Diagnosis

Summary

- A definitive diagnosis of Lyme disease can be made by culturing *B. burgdorferi* from cutaneous lesions such as EM, acrodermatitis chronica atrophicans, and borrelial lymphocytoma, or from cerebrospinal fluid on Barbour-Stoenner-Kelly medium.
- More commonly, two-tier serologic algorithm using ELISA followed by Western blot assay with associated clinical symptoms is the accepted standard for diagnosis [4, 13, 62].
- Patients usually test positive for IgM in Western blots for *B. burgdorferi* in early disease and for IgG after 4–6 weeks of exposure (Table 26.2) [18, 25, 63–65].

Culture of *Borrelia burgdorferi* from EM lesions, acrodermatitis chronica atrophicans, borrelial lymphocytoma, or cerebrospinal fluid on Barbour-Stoenner-Kelly medium provides a definitive diagnosis of Lyme disease, although this is not commonly performed and is not necessary for a diagnosis of Lyme disease [13]. Synovial fluid analysis reveals inflammatory white cell counts ranging from approximately 10,000 to 25,000 cells/mm^3. It is also common to see elevated inflammatory markers, but peripheral white blood cell counts are usually normal [4]. Alternatively, cases of Lyme disease can be diagnosed either by characteristic EM lesions or serologic diagnosis using a two-tier algorithm with an initial enzyme-linked immunosorbent assay (ELISA) or, rarely, indirect immunofluorescence assay (IFA) followed by a Western blot assay, as recommended by the US Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors (Fig. 26.6) [66]. The ELISA tests quantitatively for anti-*B. burgdorferi* antibodies. If the initial ELISA or IFA is negative there is no need for further testing. If ELISA or IFA is positive or equivocal (sometimes called indeterminate), it should be followed by a Western blot test against lysates of *B. burgdorferi*

Table 26.2 Criteria for positive Western blot diagnosis of Lyme disease

Type of infection	Isotype	Bands (kDa) needed for positive diagnosis
Before 4–6 wks	IgM	Any 2: 24 (ospC), 39 (BmpA), 41 (Fla)
After 4–6 wks	IgG	Any 5: 18, 21 (ospC), 28, 30, 39 (BmpA), 41 (Fla), 45, 58 (not GroEL), 66, 93

Data from [18, 64, 65]
Ig immunoglobulin

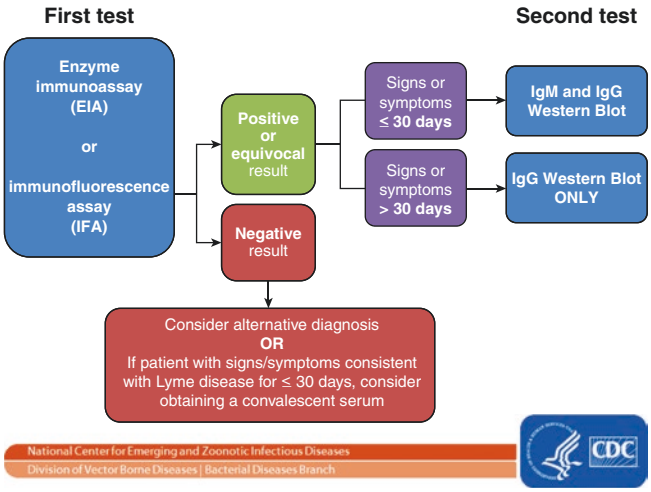

Fig. 26.6 Two-step laboratory testing for Lyme disease. The two-tier testing decision tree describes the steps required to properly test for Lyme disease. (From Centers for Disease Control and Prevention [66]. Available from https://www.cdc.gov/lyme/images/twotieredtesting_600px.jpg)

(Table 26.2) [4, 18, 49, 62–65]. A negative Western blot supersedes the results of a positive ELISA or IFA.

Despite being 99% specific for a serologic diagnosis of Lyme disease, the two-tier approach cannot detect early disease, as many patients with erythema migrans alone will not have detectable antibodies [26, 67]. The pretest probability of Lyme disease is highest in patients who either have traveled to an endemic region or have a source of potential exposure to *Ixodes scapularis* and have symptoms of early-disseminated or late disease. Furthermore, repeat testing is not indicated because host immune responses persist as a result of immunologic memory; therefore, a second positive test does not necessarily indicate persistence (or eradication in the absence of a positive test) of *B. burgdorferi* infection.

Approximately 70% of patients with EM, pathognomonic of the very early phase of Lyme disease, have been found to have positive serologies at 30 days regardless of treatment with antibiotics [64, 65]. Lyme disease can be diagnosed in patients who have classic EM lesions in the absence of serologic testing because up to 50% of patients with EM lesions will have false-negative serologic test results in the early-localized phase of infection [13, 44]. Successful treatment with antibiotics in early Lyme disease may preclude seroconversion against *Borrelia* antigens [65]. After 4–6 weeks of symptoms, it is rare to have a negative serologic response; for this reason, antibiotic treatment for Lyme disease is not recommended in patients with vague viral symptoms for more than 1 month and in whom Lyme serologic testing has remained negative [68]. In theory, there is a clinical window of time before seroconversion within the first 4 weeks of a viral syndrome particularly in an endemic region and in the absence of classic EM lesions [13].

Patients may test positive only for IgM in Western blots for *B. burgdorferi* early in the disease course. For example, 2–4 weeks after exposure, 70–80% of patients test positive by Western blots [25]. The requirement that 2 out of 3 IgM bands are present for a diagnosis of early-localized Lyme disease carries a higher potential for false-positive results, particularly if IgG antibodies are negative in patients who have experienced more than 4 weeks of symptoms [69]. Therefore, an isolated positive IgM is non-diagnostic and is either a false positive or a sign of previously treated early Lyme disease [4]. After 4 weeks of the syndrome, IgG antibodies should already be present in these individuals, and IgM positivity should be interpreted with a degree of reservation.

By 4–6 weeks after exposure to *B. burgdorferi*, patients with early-disseminated disease invariably have detectable IgG antibodies against *B. burgdorferi*. Patients with presumed Lyme arthritis thought attributable to late Lyme disease will have a positive IgG serology. A diagnosis of Lyme arthritis can be made with positive serologic testing in the appropriate clinical context, without synovial PCR testing. Persistently positive IgG and IgM in patients previously treated for Lyme arthritis indicates immune memory, not persistent infection [4].

IgM antibodies against *B. burgdorferi* can persist after the initial phase and can linger for up to 6 months after initial infection [70]. Therefore, identification of IgM antibodies in patients who had been previously infected by *B. burgdorferi* does not necessarily mean a new infection. Among 40 patients with early Lyme disease 10–20 years prior, 10% still had IgM responses and 25% had IgG responses [71]. Finally, patients who have received the Lyme vaccine may have false-positive ELISA and Western blot testing results [72].

Newer Diagnostic Tests

Summary

- Newer diagnostic tests for Lyme disease include the VIsE C6 epitope test instead of ELISA and PCR tests for *B. burgdorferi* DNA in the synovial fluid or cerebrospinal fluid for Lyme arthritis or neurologic Lyme disease [73, 74].

A newer screening test called the VIsE C6 peptide ELISA (or C6 test) is also commonly used instead of the first-tier enzyme-linked immunosorbent assay (ELISA) and can be considered a replacement for the traditional Lyme immunoglobulin (Ig) M/IgG as the initial screening test. It is derived from a conserved epitope that is found in *Borrelia burgdorferi*, *B. garinii*, and *B. afzelii* and may be an appropriate test as the initial screening prior to a Western blot [73, 74]. IgG antibodies to the C6 invariant region develop within the first week of infection, which yields a potential advantage for patients who have not yet mounted a traditional IgM response. Its specificity for Lyme disease was found to be 96% compared to 99% for a complete two-tier assay [73].

Polymerase chain reaction (PCR) tests are available for *B. burgdorferi* DNA in the synovial fluid or cerebrospinal fluid in patients with Lyme arthritis or neurologic Lyme disease. PCR findings help diagnose Lyme disease and add confirmatory information but are not a requirement for confirming the diagnosis. By itself, a positive PCR does not prove a patient has an active infection, since the *B. burgdorferi* DNA can remain after eradication has occurred. Adequate treatment with antibiotics usually eradicates PCR evidence of *B. burgdorferi* in the joints although patients may experience persistent synovitis. It is challenging to culture *B. burgdorferi* from synovial fluid because of the inflammatory environment within the joint [4]. The clinical utility of synovial or cerebrospinal fluid PCR for Lyme disease is limited. As it has low sensitivity, false-negative results are common and do not exclude neurologic abnormalities or Lyme arthritis [25].

Presently, synovial fluid PCR testing is not routinely used because it has not been standardized for clinical practice given that it cannot accurately test for active infection. Clinical suspicion and a positive serology are currently sufficient to diagnose Lyme arthritis. Synovial fluid PCR can be used to further support the diagnosis but is not required [4].

Pharmacologic Treatment

Summary

- Recommendations for treating Lyme disease vary significantly with the stage of the disease (see Table 26.1) [16, 20].
- The Infectious Diseases Society of America and the American Academy of Neurology published practice guidelines for the treatment of Lyme disease in the United States in 2006 and 2007, respectively [23, 75].

Recommendations for treating Lyme disease vary considerably with the stage of the disease (see Table 26.1) [16, 20]. The Infectious Diseases Society of America and the American Academy of Neurology published practice guidelines for the treatment of Lyme disease in the United States in 2006 and 2007, respectively [23, 75].

Controlled trials have shown that extended courses of antibiotics against *Borrelia burgdorferi* are ineffective in improving overall symptoms or functional health scores among patients who have been exposed to and fully treated for Lyme disease whose symptoms persist [76, 77]. Because it is known that *B. burgdorferi* is highly sensitive and generally incapable of mounting resistance to current antibiotics, persistence of *B. burgdorferi* in the bloodstream or infected tissues such as the synovial fluid after a full course of antibiotic treatment is unlikely, and further antimicrobial treatment is not recommended [23, 75].

Early-Localized Disease

Summary

- In adults, early disease with EM plus constitutional symptoms may be treated with a course of oral [drug: doxycycline], [drug: amoxicillin], or [drug: cefuroxime axetil], which have equivalent efficacies (Table 26.3); however, [drug: doxycycline] is the preferred agent [23, 78–82].
- The Infectious Diseases Society of America recommends oral antibiotic treatment for 14–21 days in adults with early disease manifestations [23].
- Symptoms will resolve within 20 days for most patients, and EM resolves after an average of 5–6 days [80].
- Lack of response to treatment may be due to incorrect diagnosis or coinfection with other pathogenic organisms such as *Babesia* or *Anaplasma phagocytophilum* [81, 82].

Antibiotic treatment regimens for early manifestations of *Borrelia burgdorferi* infection are summarized in Table 26.3 [23].

In adults, early uncomplicated cases of EM plus constitutional symptoms may be treated with either a course of oral [drug: doxycycline], [drug: amoxicillin], or [drug: cefuroxime], which have equivalent efficacies [78, 79]. [drug: Doxycycline] is the preferred agent for the following reasons: 1) it is effective in treating potential co-infecting agents such as *Anaplasma phagocytophilum*, which causes human granulocytic anaplasmosis (previously called human granulocytic Ehrlichiosis) and 2) it has better penetration into the central nervous system. The Infectious Diseases Society of America recommends [drug: doxycycline] treatment for 10–21 days and [drug: amoxicillin] or [drug: cefuroxime] for 14–21 days in adults, depending on the response to therapy [23]. [drug: Doxycycline] is not recommended for children younger than 8 years of age or for pregnant or lactating women. In children younger than 8 years of age with early disease, 50 mg/kg per day of oral [drug: amoxicillin] divided into three doses and not exceeding 500 mg per dose can be used [23]. In the pediatric patient intolerant to [drug: amoxicillin], 30 mg/kg per day of oral [drug: cefuroxime axetil] divided into 2 doses not exceeding 500 mg per dose can be used. Similar treatment efficacy for [drug: amoxicillin] and [drug: cefuroxime] was seen with either 20 or 30 mg/kg per day [83]. However, a single treatment course of [drug: doxycycline] may be given to children younger than 8 years of age in whom alternate agents are contraindicated. Women who may be infected with Lyme disease during pregnancy should be treated according to their disease manifestations [23]. A large body of data indicates that Lyme disease during pregnancy is not associated with harm to the fetus [84–86]. [drug: Doxycycline] should be avoided during pregnancy [23].

Table 26.3 Treatment for early Lyme Disease (days to weeks after tick bite) [rating: C expert consensus]

Type	Symptom	Drug	Adult dosage	Pediatric dosage	Adverse events
Skin	EM	[drug: Doxycycline][a, b] or	100 mg PO BID × 10–21 days	Older than 8 yrs: 2 mg/kg PO BID (max: 100 mg/dose) × 10–21 days	Photosensitivity, esophageal irritation, gastrointestinal intolerance
		[drug: Amoxicillin][c] or	500 mg PO TID × 14–21 days	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 14–21 days	Rash, diarrhea
		[drug: Cefuroxime axetil][c]	500 mg PO BID × 14–21 days	30 mg/kg/day divided BID PO (max: 500 mg/dose) × 14–21 days	Rash

Data from [23]
BID twice daily, *EM* erythema migrans, *PO* orally, *TID* 3 times daily
[a]Should not be used in children younger than 8 years of age or in lactating women
[b][drug: Doxycycline] also is active against *Anaplasma phagocytophilum* and *Bartonella henselae* (which causes cat scratch fever) but not against *Babesia microti*
[c][drug: Amoxicillin] and [drug: cefuroxime] are alternatives in patients with contraindications to [drug: doxycycline]

In the United States, macrolides ([drug: azithromycin], [drug: clarithromycin], and [drug: erythromycin]) are not recommended as first-line agents because they are less effective than [drug: amoxicillin] for EM [23, 87], and some strains of *B. burgdorferi* may be resistant to macrolides [88, 89]. Macrolides should be reserved for patients intolerant to [drug: doxycycline], [drug: amoxicillin], and [drug: cefuroxime] and for those who require close longitudinal follow-up for treatment response or progress into later stages of Lyme disease [23, 75].

Most patients have resolution of symptoms within 20 days; EM resolves after an average of 5–6 days [80]. Other mild subjective symptoms such as headache, myalgias, arthralgia, and fatigue may persist from weeks to months and may resolve spontaneously within 6 months without additional antibiotic treatment. Prolonged subjective symptoms may fall into the category of posttreatment Lyme Disease Syndrome (PTLDS). A small percentage of patients with multiple EM lesions can experience worsening of symptoms 24 hours after starting antibiotic therapy due to the release of large quantities of cytokines as the infecting bacteria are cleared from the circulation, a phenomenon known as Jarisch-Herxheimer reaction [38, 90, 91].

Lack of response to treatment may be due to the following causes:

- Incorrect diagnosis [81, 82].
- Coinfection with another agent such as *Babesia* or *Anaplasma phagocytophilum* transmitted by *Ixodes* ticks.
- Persistent alternative conditions such as patellofemoral joint disease, osteoarthritis, fibromyalgia, depression, or other clinical etiologies not related to Lyme disease.
- Persistent knee synovitis from Lyme disease after antibiotic treatment, possibly resulting from a reactive autoimmune process [92].
- Permanent tissue damage from previous neurologic damage.

Early-Disseminated Disease

Summary

- IDSA guidelines for the initial treatment of Lyme arthritis include a 30-day course of oral [drug: doxycycline] 100 mg twice daily or [drug: amoxicillin] 500 mg three times daily. IV [drug: cefuroxime axetil] 500 mg twice daily may be used in patients unable to tolerate oral medications (Table 26.4) [4, 23, 38, 75].
- 90% of patients respond to a single course of antibiotics.
- The most commonly recommended regimen for the neurologic manifestations of early-disseminated disease is 2 g IV [drug: ceftriaxone] daily for at least 2 weeks in adults (Table 26.4) [23, 75, 93–96].
- For Lyme carditis, patients with asymptomatic first-degree AV block and PR interval < 300 msec may be managed with the same oral therapy that is used for uncomplicated Lyme disease without neurologic involvement (Table 26.4) [23, 75].
- The IDSA and the AAN recommend a treatment duration of 14 days for acute neurologic Lyme disease [23, 75].

Rheumatologic manifestations are common in the early-disseminated phase of Lyme disease. IDSA guidelines for the initial treatment of Lyme arthritis include a 30-day course of oral [drug: doxycycline] 100 mg twice daily or [drug: amoxicillin] 500 mg three times daily. IV [drug: cefuroxime axetil] 500 mg twice daily may be used in patients unable to tolerate oral medications. Unless there are simultaneous neurological symptoms, the initial treatments include oral regimens as they are safer and less expensive [4].

Early-disseminated disease is characterized by acute neurologic manifestations including meningitis, cranial neuropathy (facial nerve palsy), and mononeuropathy multiplex, which require more intensive treatment. A small proportion of patients have cardiac involvement such as atrioventricular [AV] conduction deficit and myopericarditis (Table 26.4) [23, 75].

Resolution of neurologic symptoms is often delayed, and persistent symptoms are not indicative of treatment failure. Some practitioners favor using a longer course (21–28 days) of antibiotics particularly when there is evidence of more severe neurologic symptoms [75].

Late Disease

Summary

- The majority of patients with Lyme arthritis will respond to a single course of antibiotics.
- Antibiotic-refractory Lyme arthritis may occur in rare cases after 2–3 months of oral or intravenous therapy; symptomatic therapy is recommended for such cases (Table 26.5) [23].

Table 26.4 Treatment for early-disseminated Lyme disease (days to weeks after tick bite) [rating: C expert consensus]

Type	Symptoms	Drug	Adult dose	Pediatric dose	Adverse events
Neurologic disease	Isolated facial nerve palsy, meningitis, or radiculoneuropathy (early-disseminated disease)	[drug: Doxycycline][a, b]	100 mg PO BID × 14 to 28 days	Older than 8 yrs: 4.4 mg/kg PO BID (max: 100 mg/dose) × 14–28 days	Photosensitivity, esophageal irritation, gastrointestinal intolerance
		[drug: Amoxicillin][c]	500 mg PO TID × 14–21 days	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 14–21 days	Rash, diarrhea
		[drug: Cefuroxime][c]	500 mg PO BID × 14–21 days	30 mg/kg/day divided BID PO (max: 500 mg/dose) × 14–21 days	Rash
	More serious disease (encephalitis, early with parenchymal or late disseminated)	[drug: Ceftriaxone][d, e]	2 g IV QD × 28 days (range: 14–28 days)	50–75 mg/kg IV QD (max: 2 g/dose) × 28 days (range 14–28 days)	Diarrhea, biliary complications
Cardiac disease	Mild (first-degree AV block, PR interval < 300 msec)	[drug: Doxycycline][a, b]	100 mg PO BID × 21 days (range: 14–21 days)	Older than 8 yrs: 4.4 mg/kg PO BID (max: 100 mg/dose) × 21 days (range: 14–21 days)	Photosensitivity, esophageal irritation, gastrointestinal intolerance
		[drug: Amoxicillin][c]	500 mg PO TID × 21 days (range: 14–21 days)	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 21 days (range: 14–21 days)	Rash, diarrhea
		[drug: Cefuroxime axetil][c]	500 mg PO BID × 21 days (range: 14–21 days)	30 mg/kg/day divided BID PO (max: 500 mg/dose) × 14–21 days	Rash
	More serious disease (symptomatic, second- or third-degree AV block, or first-degree AV block with PR interval ≥ 300 msec)	[drug: Ceftriaxone][d, e, f]	2 g IV QD 14 to 28 days	50–75 mg/kg IV QD (max: 2 g/dose) × 21–28 days	Diarrhea, biliary complications
Eye	Conjunctivitis (in case of influenza-like disease)	[drug: Doxycycline][a, b]	100 mg PO BID × 14 days	Older than 8 years: 2 mg/kg PO BID (max: 100 mg/dose) × 14 days	Photosensitivity, esophageal irritation, gastrointestinal intolerance
		[drug: Amoxicillin][c]	500 mg PO TID × 14 days	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 14 days	Rash, diarrhea
		[drug: Cefuroxime][c]	500 mg PO BID × 14 days	30 mg/kg divided BID PO (max: 500 mg/dose) × 14 days	Rash
Musculo-skeletal	Arthritis (without neurologic disease)	[drug: Doxycycline][a, b]	100 mg PO BID × 28 days	Older than 8 years: 4.4 mg/kg BID PO (max: 100 mg/dose) × 28 days	Photosensitivity, esophageal irritation, gastrointestinal intolerance
		[drug: Amoxicillin][c]	500 mg PO TID × 28 days	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 28 days	Rash, diarrhea

Data from [23, 75]

BID twice daily, *IV* intravenous, *PO* orally, *QD* once daily, *TID* 3 times daily

[a]Should not be used in children younger than 8 years of age or in lactating women

[b][drug: Doxycycline] has also activity against *Anaplasma phagocytophilum* and *Bartonella henselae* (which causes cat scratch fever) but not against *Babesia microti*

[c][drug: Amoxicillin] and [drug: cefuroxime] are alternatives in patients with contraindications to [drug: doxycycline]

[d]In non-pregnant adult patients intolerant to beta-lactam antibiotics, [drug: doxycycline] 200–400 mg per day PO or IV in 2 divided doses. In children older than 8 years of age, [drug: doxycycline] 4–8 mg/kg per day in 2 divided doses to a maximum daily dose of 200–400 mg

[e]Or [drug: cefotaxime] 2 g IV every 8 hours × 14–28 days for adults and 150–200 mg/kg/day in 3 divided doses (maximum 6 g per day) for children or [drug: penicillin G] 18–24 million U per day divided into doses given every 4 hours in adults and 200,000–400,000 U/kg per day divided every 4 hours (maximum 18–24 million U per day) in children

[f]A parenteral antibiotic regimen is recommended for initiation of treatment of hospitalized patients. IV antibiotics should be continued until high-grade AV block has been resolved and PR interval is <300 msec. The patient should complete a 21- to 28-day course. A temporary pacemaker may be necessary

Table 26.5 Treatment for late stages of Lyme disease (months to years after tick bite) [rating: C expert consensus]

Type	Symptoms	Drug	Adult dose	Pediatric dose
Neurologic disease	More serious disease (meningoradiculoneuritis, encephalitis)	[drug: Ceftriaxone]	2 g IV QD × 14–28 days	50–75 mg/kg IV QD (max: 2 g/dose) × 14–28 days
Musculoskeletal	Arthritis with neurologic disease	[drug: Ceftriaxone]	2 g IV QD × 28 days	50–75 mg/kg IV QD (max: 2 g/dose) × 14–28 days
	Persistent arthritis (despite prior oral therapy)	[drug: Doxycycline]	100 mg PO BID × 28 days	Older than 8 yrs of age: 4.4 mg/kg PO BID (max: 100 mg/dose) × 28 days
		[drug: Amoxicillin]	500 mg PO TID × 28 days	50 mg/kg/day PO divided TID (max 500 mg/dose) × 28 days
		[drug: Ceftriaxone]	2 g IV QD × 14–28 days	50–75 mg/kg IV QD (max: 2 g/dose) × 14–28 days

BID twice daily, *IV* intravenous, *PO* orally, *QD* once daily, *TID* 3 times daily
Data from [23]

Table 26.6 Treatment for persistent Lyme arthritis refractory to first antibiotic treatment (months to years after tick bite) [rating: C expert consensus]

Musculoskeletal symptoms	Drug	Adult dosage	Pediatric dosage
Limited inflammation (monoarthritis)	May repeat: [drug: Doxycycline]	100 mg PO BID × 28 days	Older than 8 yrs of age: 4.4 mg/kg PO BID (max: 100 mg/dose) × 28 days
	[drug: Amoxicillin]	500 mg PO TID × 28 days	50 mg/kg/day divided TID PO (max: 500 mg/dose) × 28 days
Significant inflammation (effusion, limited range of motion, oligoarthritis)	May repeat: [drug: Ceftriaxone]	2 g IV QD × 28 days	50–75 mg/kg IV QD (max: 2 g/dose) × 14–28 days
	[drug: Cefotaxime]	2 g IV every 8 hrs × 28 days	150–200 mg/kg/day in 3 divided doses (max: 6 g/day) × 14–28 days
	[drug: Penicillin G]	18–24 million U/kg/day IV divided every 4 hrs × 28 days	200,000–400,000 U/kg/day divided every 4 hrs (max: 18–24 million U/day) × 28 days
Remission not reached, *Borrelia burgdorferi* DNA not present in synovial fluid	NSAIDs, DMARD (methotrexate or hydroxychloroquine), arthroscopic synovectomy	–	–

DMARD disease-modifying antirheumatic drug
Data from [23]

Arthritis and neurologic findings (encephalopathy, peripheral neuropathy, and encephalomyelitis) are late manifestations of Lyme disease. Treatment approaches are shown in Table 26.5 [23].

Arthritis can usually be treated successfully with 1 month of oral [drug: doxycycline] or [drug: amoxicillin]; 90% of patients respond to a single course of antibiotics [38]. If symptoms improve but do not resolve, or if mild synovitis remains, a second course of oral antibiotics for 30 more days is recommended. Patients without improvements or persistent moderate to severe synovitis may require intravenous therapy with [drug: ceftriaxone] (2 g once daily for 14–28 days) (Table 26.5) [23, 79]. IV therapy for 4 weeks has been shown to have greater efficacy. However, IV therapy beyond 30 days has no additional benefit at the cost of increased adverse events [4]. Adjunctive therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy may be beneficial. Re-aspiration of the affected joint may be required. Intra-articular steroid injections are not recommended before antibiotic therapy because they may delay the resolution of Lyme arthritis [23].

In rare cases, antibiotic-refractory Lyme arthritis may occur after 2–3 months of oral or intravenous therapy and likely result from infection-induced autoimmunity triggered by retained spirochetal antigens rather than ongoing infection [97–101]. There are genetic, immunologic, and pathogen-specific factors that may place patients at risk for antibiotic-refractory Lyme arthritis. These include certain HLA-DR alleles, the TLR1-1805GG polymorphism, ECGF autoantibodies, and the highly inflammatory RST-1 strain of *B. burgdorferi* as previously described [4]. In such cases, symptomatic therapy is recommended (Table 26.6) [23].

These patients may require treatment with NSAIDs, Disease Modifying Anti-Rheumatic Drugs (DMARDs), and in some cases Tumor Necrosis Factor (TNF) inhibitors. Oral or intra-articular corticosteroids should be avoided until the antibiotic course is completed as they may result in greater spirochetal growth. Some studies have shown intra-articular corticosteroids may increase the duration of arthritis [4].

[drug: Methotrexate] (15–20 mg/week) and [drug: hydroxychloroquine] (400 mg daily) have been successful treatments in clinical practice but have not been validated

through randomized controlled trials. DMARD therapy is used for 6–12 months, as longer courses are typically unnecessary. There are reports showing efficacy of TNF inhibitors such as [drug: etanercept] and [drug: adalimumab] in the treatment of antibiotic-refractory Lyme arthritis for patients with incomplete responses to [drug: methotrexate] [4].

MRI with contrast may be useful in some cases of refractory Lyme arthritis. Imaging may reveal synovial hypertrophy and enhancement, reflecting underlying inflammation. Arthroscopic synovectomy may be considered in these patients with monoarticular Lyme arthritis with incomplete response to DMARD therapy [4].

Late neurologic manifestations are relatively rare, and treatment recommendations are based on small studies [102, 103]. Acrodermatitis chronica atrophicans, which manifests as progressively fibrosing skin, is caused by continuous infection and is typically treated with the same oral antibiotic regimen used for early Lyme disease [23, 104, 105].

Posttreatment Lyme Disease Syndrome (PTLDS)

Summary

- Posttreatment Lyme disease syndrome (PTLDS) is difficult to treat, and randomized controlled trials of repeated courses of antibiotic therapy have not shown any additional benefits [76, 77, 106–111].
- Chronic subjective symptoms that persist after a recommended course of antibiotic therapy are not due to persistent infection with *Borrelia burgdorferi.*

Some patients with Lyme disease have persistent mild subjective symptoms such as fatigue, headaches, musculoskeletal pain, arthralgias, and cognitive complaints that may persist for weeks to months despite appropriate antibiotic treatment [17, 78, 80, 110]. The Infectious Diseases Society of America [23], the American Academy of Neurology [75], and the Ad Hoc International Lyme Disease Group [44] concluded that the chronic subjective symptoms that persist after a recommended course of antibiotic therapy are not due to persistent infection with *Borrelia burgdorferi*. PTLDS is difficult to treat, and randomized controlled trials of repeated courses of antibiotic therapy with or without [drug: hydroxychloroquine] have not shown any additional benefits [76, 77, 106–111].

Conclusion

Summary

- Lyme disease is caused by organisms of the pathogen complex *B. burgdorferi* sensu lato and transmitted by the hard tick *Ixodes scapularis* [1, 2].
- Transmission increases from late spring through fall, with peaks in June and July.
- Three clinical phases are recognized: early-localized, early-disseminated, and late Lyme disease.
  - The most common manifestation of early-localized phase is erythema multiforme [23, 24].
  - Rheumatologic manifestations are common in early-disseminated phase [36, 37].
  - Lyme arthritis occurs during late disease in 60% of untreated patients [4, 25, 44, 45].
- EM is diagnostic for early Lyme disease in the absence of serologic confirmation [23, 24].
- Treatment with [drug: doxycycline] and [drug: amoxicillin] or [drug: cefuroxime] typically resolves symptoms within 20 days, although some patients have persistent symptoms after treatment [23].
- Lyme arthritis can usually be treated successfully with 1 month of oral antibiotics. If symptoms do not fully resolve, a second course of oral antibiotics is recommended [38].
- In rare cases, antibiotic-refractory Lyme arthritis may occur after 2–3 months of oral or intravenous therapy [4, 38].
  - These patients may require treatment with NSAIDs, DMARDs, and in some cases TNF inhibitors [4].

Lyme disease, caused by organisms of the pathogen complex *Borrelia burgdorferi* sensu lato and transmitted by the hard tick *Ixodes scapularis*, is the most common vector-borne infection in the United States. Endemic regions include the northeastern and mid-Atlantic states, the north central states, and states along the Pacific coast (see Fig. 26.3) [15]. Infection rates increase from late spring through fall with peaks between the months of June and July [12], and most *B. burgdorferi* infections occur in individuals 5–15 years and 45–55 years of age [14].

Three clinical phases are recognized: early-localized, early-disseminated, and late Lyme disease. Erythema migrans, the telltale bull's-eye rash, is the most common clinical manifestation of early-localized Lyme disease [23,

24]. Other early symptoms include malaise, fatigue, headache, fever, and lymphadenopathy [25]. Typical symptoms of the early-disseminated phase include inflammatory arthritis and synovitis [36, 37]. Lyme arthritis is characteristic of the late phase of disease, occurring in 60% of untreated patients [4, 25, 44, 45]. The presence of EM lesions is diagnostic for early Lyme disease in the absence of serologic confirmation. Definitive diagnosis is made by identification of *B. burgdorferi* in cultured EM lesions or by enzyme-linked immunosorbent assay and Western blot [13, 62].

For adults with confirmed Lyme disease confined to the skin, the recommended treatment is a 10- to 21-day course of [drug: doxycycline] or [drug: amoxicillin] or [drug: cefuroxime] for 14–21 days] [23]. Symptoms typically resolve within 20 days with antibiotic therapy. Lyme arthritis can usually be treated successfully with 1 month of oral antibiotics. If symptoms do not fully resolve, a second course of oral antibiotics is recommended. In rare cases, antibiotic-refractory Lyme arthritis may occur after 2–3 months of oral or intravenous therapy and may require immunosuppressive treatment [4, 38]. Chronic subjective symptoms after appropriate courses of antibiotic treatment for Lyme disease do not reflect active infection with B. *burgdorferi*, and repeat treatment is not recommended [4, 23, 75].

Coinfection with other tick-borne organisms, including *B. miyamotoi*, *Anaplasma phagocytophilum,* or *Babesia microti*, should be suspected when fever persists despite appropriate antibiotics against *B. burgdorferi* or in the presence of unexplained liver enzyme abnormalities or hemolysis, especially in asplenic patients. It is important for primary care clinicians to recognize the symptoms of all stages of Lyme disease and refer patients to a rheumatologist for management of any articular manifestations [23].

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Mycoplasmal Arthritis

27

Luis E. Vega and Luis R. Espinoza

Mycoplasmas are free-living microorganisms that lack a cell wall around their cell membrane. They belong to the Mollicutes class and genus Mycoplasma in the family mycoplasmataceae. These species have some features that differ from other bacteria:

- Lack of a cell wall
- Extremely small genome
- Limited capacity for biosynthesis
- Sensitivity to environmental factors
- Resistance to β lactam antibiotics
- Fastidious growth requirements

They are ubiquitous and live in humans, animals, plants, and insects. They are primarily commensals residing on mucosal surfaces (mouth, upper respiratory tract, lower urogenital tract, cervix, and vagina) as part of the microbiome in healthy people but also can induce several diseases of the respiratory and genitourinary tracts and joints [1, 2].

There are more than 200 known species in Mollicutes class (cell wall–free bacteria) but at least 16 of these species have been isolated from humans except those of animal origin that have been isolated occasionally from immunosuppressed humans [2, 3] (Table 27.1).

In humans, there are at least six species of main importance because they are considered either as primary pathogens or opportunists: *Mycoplasma pneumoniae* (Mpn) causes pneumonia and has been associated with joint and other infections. *Mycoplasma hominis* (Mho) sometimes causes postpartum fever and has been found with other bacteria in urogenital infections such as pyelonephritis, pelvic inflammatory diseases, and vaginosis. *Ureaplasma urealyticum* is a causal agent of nongonococcal urethritis, acute prostatitis (in men), and is associated with lung disease in premature infants of low birth weight. *Mycoplasma genitalium* (Mg) is closely related to M. pneumoniae and has been associated with urethral and other urogenital infections; *Mycoplasma fermentans* (Mf) is considered as an opportunist pathogen in HIV-infected patients and is associated with chronic arthritis. *Ureaplasma parvum* (Up) is associated with a variety of clinical conditions including urethritis, arthritis, chorioamnionitis, postpartum endometritis as well as pre-term birth, pneumonia, meningitis, and chronic lung disease in neonates [4–8].

There are other mycoplasmas probably related to the development and outcome of AIDS patients such as

Table 27.1 Mycoplasmas and ureaplasmas isolated from human beings

Site and species	Frequency of isolation	Associated with disease
Respiratory tract		
M. pneumoniae	Rare	Yes
M. orale	Common	No
M. salivarium	Common	No
M. hominis	Rare	Questionable
U. urealyticum	Rare	Questionable
M. buccale	Rare	No
M. faucium	Rare	No
A. laidlawaii	Rare	No
Urogenital tract		
M. hominis	Common	Yes
U. urealyticum	Common	Yes
M. pneumoniae	Rare	Yes
M. fermentans	Rare	Yes
M. primatum	Rare	No
M. salivarium	Rare	No
Synovial fluid		
M. hominis	Unknown	Yes
U. urealyticum	Unknown	Yes
M. pneumoniae	Unknown	Yes
M. fermentans	Questionable	Questionable
M. arthritides	Questionable	Questionable
M. hyorhinis	Questionable	Questionable

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_27

Mycoplasma genitalium (Mg), *Mycoplasma fermentans* (Mf), *Mycoplasma penetrans* (Mpe), *Mycoplasma pirum* (Mpi), also called AIDS-associated mycoplasmas, but need further studies [9].

At present, some mycoplasma species are known to be pathogenic in human beings and the joints can be affected [10]. Published cases have been reported about patients affected with septic arthritis and reactive arthritis in immunocompetent and immunosuppressed individuals.

Arthritis Associated with *Mycoplasma pneumoniae* Infections

Pneumonia has been a hallmark of *Mycoplasma pneumonia* infection; however, also other extrapulmonary diseases may be induced (Table 27.2).

The pathogenic mechanisms of extrapulmonary diseases due to *Mycoplasma pneumoniae* have not been elucidated yet. These mechanisms may be by direct action in which locally induced cytokines play a role or indirect in which autoimmunity is the causal phenomenon [11].

There are several reports about this association. The first report was made in 1968, and since then numerous reports have appeared in the literature. Arthritis may accompany *Mycoplasma pneumonia* respiratory infection in as many as 16% of cases. The onset of articular involvement is acute and transient and recovery is complete within the acute phase of illness or may be severe and last for up to 18 months. The pattern of disease is monoarticular or migratory and polyarticular with the larger joints affected more often than the smaller ones. *Mycoplasma pneumonia* has been isolated from synovial fluid of affected joints in all reported cases, and all were immunocompetent patients [12–15].

Table 27.2 Extrapulmonary symptoms due to *M. pneumoniae*

Symptoms	Direct	Autoimmunity
Cardiovascular	Pericarditis, endocarditis	Myocarditis, Kawasaki disease
Dermatological	Stevens-Johnson syndrome	Erythema multiforme, urticarial anaphylactoid purpura
Liver	Hepatitis (early)	Hepatitis (late)
Hematological		Autoimmune hemolytic anemia, hemophagocytic syndrome, thrombocytopenic purpura, infectious mononucleosis
Musculoskeletal	Arthritis	
Neurologic	Encephalitis, myelitis, aseptic meningitis	
Oto-ocular	Otitis media	Conjunctivitis, iritis, uveitis
Kidney		Glomerulonephritis, IgA nephropathy

Arthritis Associated with Genital Mycoplasmal Infections

A brief review of species that colonize the urogenital tract is appropriate [4, 16]. Of the species of mycoplasmas isolated from the urogenital tract of humans, four are found to cause disease: *M. hominis, M. genitalium, U. urealyticum, and U. parvum* (Table 27.3).

M. hominis

This mycoplasma colonizes the cervix or vagina in 21–53% of asymptomatic sexually active women, but this frequency is lower in the male urethra. Often, they are concurrently present with ureaplasma species. The mode of transmission is venereal and vertical.

M. genitalium

This mycoplasma species was initially isolated from urethritis in man. Unlike other genital mycoplasmas that are rather common as commensals in the lower urogenital tract of many healthy adults, the presence or detection of mycoplasma genitalium is associated with clinical infection.

Table 27.3 Diseases associated with mycoplasmas and ureaplasmas

Disease	Mycoplasma or Ureaplasma species	Association
Nongonococcal urethritis	*M. genitalium* *U. urealyticum*	3 2
Epididymitis	*U. urealyticum*	1
Pelvic inflammatory disease	*M. hominis*	1
Postpartum fever	*M. hominis* *U. urealyticum*	3 3
Pyelonephritis	*M. hominis*	2
Stones	*U. urealyticum*	2
Various conditions in immunosuppressed patients	*M. hominis*	3
Pneumonitis in children and adults	*M. pneumoniae* *M. fermentans*	4 1
Pneumonia and chronic lung disease in low birth weight infants	*U. urealyticum*	3
Arthritis in immunocompetent patients	*M. fermentans* *M. genitalium*	2 1
Sexually acquired reactive arthritis	*U. urealyticum*	2
Arthritis in immunosuppressed and hypogammaglobulinemic patients	*M. hominis* *Ureaplasma* species	4 4

Association 0 = none, 1 = weak, 2 = moderate, 3 = strong, 4 = very strong

M. fermentans

This mycoplasma was isolated from the human urogenital tract and named before the 1980s as the "incognitus strain" and was detected in tissues of patients with AIDS and led to the belief that they might be important in the development of AIDS.

Ureaplasma urealyticum and *Ureaplasma parvum*

These species found in humans may harbor in the cervix or vagina in 40–80% of healthy adult women. This frequency is less in the lower urogenital tract of healthy men. The mode of transmission of these species is venereal and vertical, either in utero or during delivery of the neonate. *U. parvum* is more common than *U. urealyticum* as a colonizer of the male and female urogenital tracts and in the neonatal respiratory tract.

The cases of articular diseases reported are septic arthritis and reactive arthritis. The onset is acute, and the clinical patterns of disease are monoarticular, oligoarticular, or polyarticular. Individuals affected can be immunocompetent and/or immunosuppressed.

Reactive Arthritis

The most frequent clinical manifestation of mycoplasma-related disease is on the musculoskeletal system as asymmetrical oligoarthritis localized in lower extremities, present in 69.4% of patients. *Chlamydia trachomatis* can be found in the synovial fluid in 54% of patients (20/37), ureaplasma or mycoplasma was isolated in the synovial tissue of 73.1% of patients (30/41), and in the peripheral blood mononuclear cells in 93.2% of patients (41/44). Human leukocyte antigen B27 was present in 83.3% of patients [17].

Mycoplasma genitalium is an important cause of sexually transmitted infections that is gaining recognition and is an independent cause of acute and chronic nongonococcal urethritis in men. *M. genitalium* has been implicated as a possible causative factor in reactive arthritis. Reactive arthritis complicating *M. genitalium* urethritis in an HLA-B27-positive patient has been reported [18].

Arthritis in Special Situations

Septic arthritis can occur as a complication of infection by these mycoplasmas in special situations. Patients with hypoagammaglobulinemia are probably more susceptible to colonization of their mucous surface, especially of the urogenital tract with mycoplasma species. This colonization would increase the likelihood for microorganisms to disseminate to distant sites such as joints. Furr et al. reported that mycoplasma species are responsible for septic arthritis in approximately 38% cases [19]. Affected individuals may develop septic arthritis that lasts from several months to over a year. In all cases, mycoplasma was isolated [20]. Other situations are patients with leukemia, hypocomplementemia, or on chemotherapy, glucocorticoids, immunosuppressive therapy, prosthetic joint, and urinary tract instrumentation [21–23]. Sometimes the arthritis may be persistent and destructive due to resistance to multiple antibiotics.

Association with Diffuse Connective Tissue Disease: Rheumatoid Arthritis

An infectious etiology for rheumatoid arthritis has long been considered, and this has led to speculation about the potential role of mycoplasmas in its development. Their arthritogenic potential was strengthened by reports that described isolation from the joints of such patients, but subsequent reports have questioned those initial findings [3].

At present, this etiologic possibility cannot be completely discarded, and it is possible to state that rheumatoid arthritis might be a manifestation of the response to an infectious agent including mycoplasma in a genetically susceptible host.

Some clues that link mycoplasma and rheumatoid arthritis are the findings from Ramirez et al. [24]. They observed an interesting relationship between rheumatoid arthritis and antibodies against *Mycoplasma pneumoniae*. Patients with rheumatoid arthritis had higher antibody titers compared with controls. Another clue supporting this association is the well-known and successful use of minocycline in the treatment of rheumatoid arthritis, which is also an effective antibiotic against mycoplasmal infections [25, 26].

M. fermentans has also been considered an inducer agent of rheumatoid arthritis and other arthritides because it has been found in synovium and synovial fluid of patients with rheumatoid arthritis and in some cases of spondyloarthritis [27–31].

Rivera et al. induced experimental arthritis in rabbits following inoculation of *Mycoplasma fermentans*, and this finding could explain the role of these bacteria in the genesis of arthritis [32].

Diagnosis

Clinical findings and laboratory tests allow us to make a diagnosis of mycoplasma infection. Because several mycoplasma species are commensals in the respiratory tract, lower urogenital tract, cervix, and vagina of healthy people their isolation should be interpreted with caution. A positive result may not be meaningful in the absence of clinical manifestations. We always must correlate the presence of clinical findings and laboratory findings because occasional asymptomatic carriers

may exist. The presence of mycoplasmas in normally sterile extragenital or extrapulmonary sites should be considered diagnostic of clinically significant infection (joints, cerebrospinal fluid).

Applying a strict definition, a diagnosis of mycoplasmal arthritis should be considered in the following situations:

- Any patient with antecedent of documented mycoplasmal infection.
- Any patient in which Gram's stains are negative and no common bacterium isolated.
- Any patient with hypo-agammaglobulinemia, leukemia, hypocomplementemia, chemotherapy, glucocorticoid and immunosuppressive therapy, prosthetic joint, and urinary tract instrumentation.

Culture

Mycoplasmas are free-living microorganisms, fastidious to grow, and demanding in their requirements for special media. The following media are available [2, 33, 34]:

- SP4 broth: *P. pneumoniae*, *M. hominis*
- 10B and A8 broth: *Ureaplasma urealyticum*

M. hominis and *Ureaplasma* species grow in culture within 1–3 days. *M. pneumoniae* requires 5 days to grow. A negative culture does not necessarily exclude the diagnosis because of the presence of a low organism load in the sample or the presence of inhibitors liberated from disrupted cells. In this situation, we should complement with other tests.

Serology

Serum and synovial fluid should be analyzed for the presence of antibodies. Serological testing was the first method developed for the detection of *Mycoplasma pneumoniae* infection. At present, there are other serological tests: complement fixation, enzyme immunoassays, immunofluorescence, and particle agglutination assays. The main disadvantages of serological tests are as follows [34]:

- Need to wait 1–2 weeks from onset of the infection until detectable antibody develops.
- Requirement of serum samples both for acute and convalescent phase. Serum samples that are tested simultaneously for IgM and IgG. This is to confirm seroconversion.
- Difficulty in distinguishing current infection from a past infection.

Testing for IgG in addition to IgM in paired serum specimens produces better diagnostic yields than those obtained by the complement fixation test (CFT) and the microparticle agglutination (MAG) assay [35].

Chen et al. compared the performance of chemiluminescence immunoassay (CLIA), enzyme-linked immunosorbent assay (ELISA), and the passive agglutination (PA) method in detecting *Mycoplasma pneumoniae* (MP) infection. Results showed that CLIA and ELISA have a higher sensitivity compared with PA. CLIA has a high concordance with ELISA. Moreover, CLIA has a higher specificity and sensitivity for the detection of IgM and IgG and should be used for the clinical diagnosis of MP infection [36].

At present, the detection of cold agglutinins is not an important test. Cold agglutinins are IgM antibodies that are produced 1–2 weeks after initial infection in about 50% of *M. pneumoniae* infections and may persist for several weeks. Also, cold agglutinins also occur in persons who have various bacterial and rickettsial infections as well as in those with influenza virus and adenovirus infections.

Molecular-Based Tests

Polymerase chain reaction (PCR) is a technique that has advantages over serologic assays and culture for detection of mycoplasmas.

Use of polymerase chain reaction (PCR for detection of mycoplasma infection in extrapulmonary or extragenitourinary infection can also be helpful for the following reasons:

- The cultures from these sites are rarely positive as a result of low organism load.
- In early infection, insufficient time has elapsed since onset of illness for an antibody response to develop.

Theoretically, PCR is more sensitive than culture, and this has yielded contradictory results, especially in asymptomatic carriers with low bacterial load. It is very important to ascertain whether clinically significant disease is actually present [37–41].

At present, PCR is the method most widely used for detection of mycoplasmas and ureaplasmas and also has been adapted to detect antimicrobial resistance determinants [42–47]. Conventional PCR has been improved and is been replaced by real-time PCR that has advantages in accuracy, quantitation, and turnaround time [48, 49].

Treatment

Any patient with arthritis and positive synovial fluid cultures or PCR for a mycoplasma should be treated immediately with antibiotics likely to be effective against these organisms while awaiting sensitivity results that may require several days.

Mycoplasma pneumoniae is susceptible to various antibiotics such as macrolides and related antibiotics, tetracyclines, and fluoroquinolones [50]. Macrolides and related antibiotics are the first antibiotics of choice in *Mycoplasma pneumoniae* respiratory tract infections mainly because their high efficacy, their low toxicity, and their use in young children. The newer macrolides are now the preferred agents with a 7-to-14 day course of oral clarithromycin or a 5-day course of oral azithromycin for treatment of community-acquired pneumonia due to *Mycoplasma pneumoniae* [51, 52]. There are reports showing that the resistance is increased worldwide with prevalence now ranging between 0% and 15% in Europe and the USA, approximately 30% in Israel, and up to 90–100% in Asia [7, 53, 54].

There are alternative antibiotic therapies including tetracyclines such as doxycycline and minocycline or fluoroquinolones, primarily levofloxacin, during 7–14 days, even though fluoroquinolones and tetracyclines are contraindicated in all children and in children <8 years old, respectively, and in this situation erythromycin is the drug of choice.

Recently, the British Association of Sexual Health and HIV launched the guidelines for the diagnosis and management of *Mycoplasma genitalium* in people aged 16 years and older [55].

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Parasitic Arthritis

28

Javier Dario Márquez-Hernández

Introduction

Parasitic infections occur worldwide. There are significant advances and insights in the pathogenesis and treatment of these opportunistic infections. Musculoskeletal involvement secondary to parasites is important to consider in developing countries and certain geographic locations where the health system is precarious.

Well-known risk factors are immunosuppressive states (caused by medications, comorbidities, malignancies, infectious diseases such as HIV, etc.), travel to regions with ongoing parasitic endemicity, ingestion of poorly cooked food, exposure to infected blood products, congenital transmission, and laboratory or occupational exposure [1].

Since antiquity, there has been interest in the relationship between infections by parasites and joint involvement. At the beginning of the last century (1922), amoeba infection was considered the cause of the second great type of chronic arthritis: osteoarthritis [2]. At that time, it was believed that tooth infection by amoeba could invade the bones causing osteoarthritis.

Musculoskeletal involvement is seldom the initial clinical manifestation of parasitic infection; and more often, other organ systems such as gastrointestinal, skin, muscle, vascular, and central nervous systems become affected. Diarrhea, abdominal pain, lung involvement, soft tissue abscesses, vasculitis-like lesions in the skin, and stroke may be presenting clinical manifestations of parasitic infection. Disease burden of parasitic infection matters, and new techniques to identify and establish the diagnosis of parasitic musculoskeletal involvement and appropriate treatment will be discussed in this chapter. To facilitate the discussion, parasitic infection will be classified according to the classic taxonomy in as follows:

1. Protozoan, microscopic one-celled organisms, such as Sarcodina: *Amoeba*; flagellates with motion, e.g., *Giardia* or *Leishmania*; and Sporozoa, which in adult stage are not motile like *Plasmodium* or *Cryptosporidium*.
2. Helminthes or large and multicellular parasites which are visible to the naked eye. They are flatworms (platyhelminthes) including trematodes (flukes), cestodes (tapeworms), and nematodes (roundworms).

Parasitic infections are divided into two categories according to their location: endoparasites and ectoparasites. Endoparasites inhabit the internal cavities and tissues of the host and are classified as intestinal if they inhabit the alimentary canal, gallbladder, liver, and its ducts (Fig. 28.1). Ectoparasites reside on the skin and can be divided into permanent (of long duration, sometimes lifelong) and temporary (of short duration).

Protozoan Infections

Protozoa are unicellular microscopic organisms. Several agents belong to this group, some of them without motion like *Amoeba*, flagellates with motion (*Cryptosporidium* sp., *Giardia* sp., *Plasmodium* sp., *Trypanosoma* sp., *Trichomonas* sp.), or Sporozoa like spore with limited motion (*Toxoplasma* sp.).

Amoebas

These parasites often cause gastrointestinal clinical manifestations such as colicky pain and diarrhea symptoms, but rarely cause arthritis in humans. Liver abscesses and severe enteritis have been reported including case reports of fatal intestinal perforation by *Entamoeba histolytica* secondary to the use of tumor necrosis factor (TNF) inhibitors. TNF is an important cell immunity mediator against amoeba, is a potent chemotactic to *E. histolytica*, and enhances its adhe-

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_28

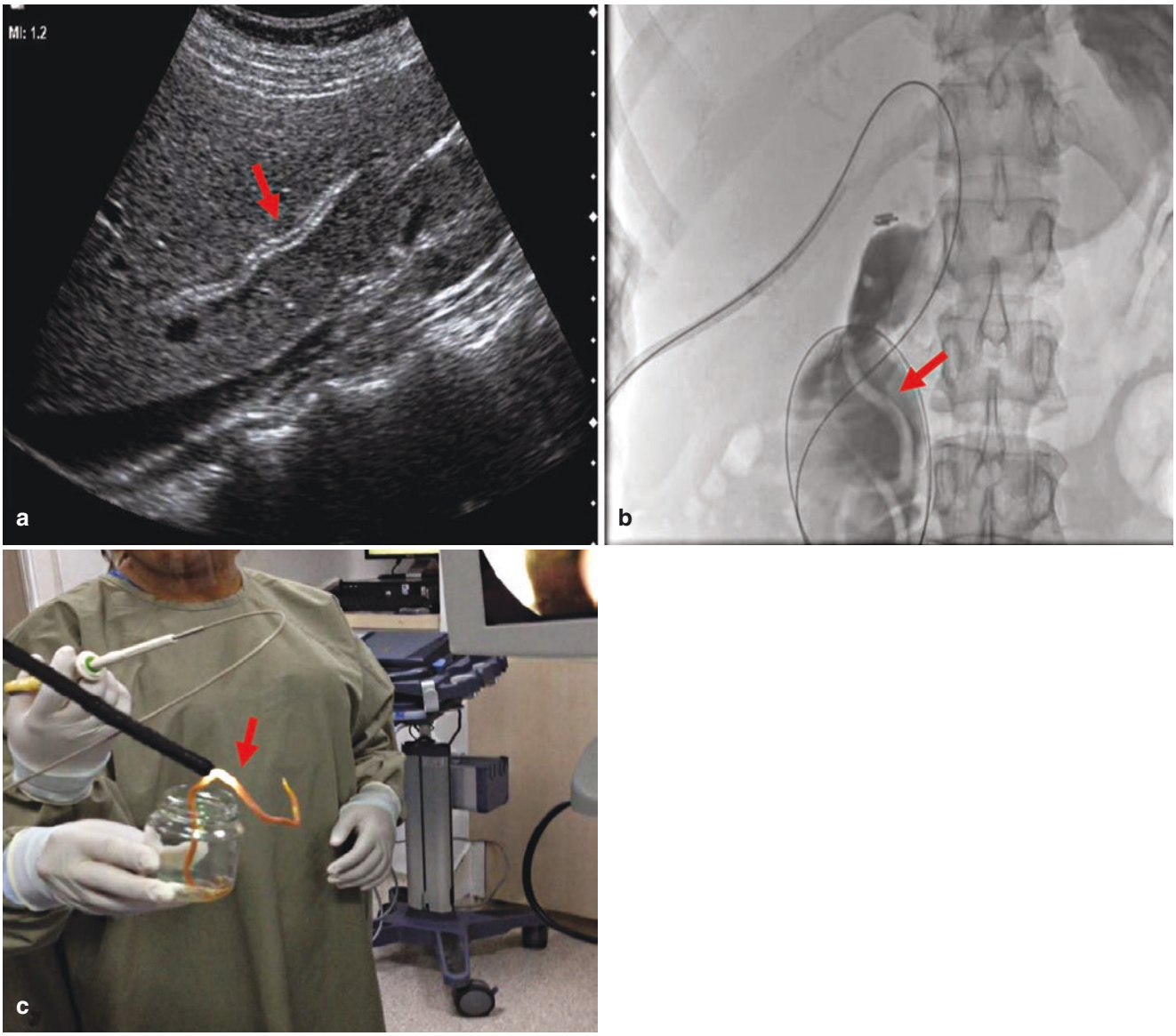

Fig. 28.1 Gallbladder ultrasound (**a**), endoscopic retrograde cholangiography (**b**), in a 42-year-old Hispanic female patient with jaundice, pain in the right hypochondrium, and suspicion of cholelithiasis. (**c**) Endoscopic removal of the parasite *(arrows)*. (Courtesy of Sergio Alvarez, MD, chief of Radiology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

sion to enterocytes by the lectin-galactose pathway and then activating macrophages to kill amoeba through the release of nitric oxide. Therefore, the use of TNF inhibitors is potentially harmful by enhancing the virulence of amoebas [3] (Fig. 28.2).

Cryptosporidium spp.

Cryptosporidium sp. is a flagellate protozoan that frequently causes diarrhea in healthy and immunosuppressed individuals worldwide. This parasite is considered as causing the second most common life-threatening diarrhea in children under 2 years of age, after viral gastrointestinal infection. *Cryptosporidium hominis* is responsible for three-quarters of the cryptosporidiosis-induced diarrhea. More than 25 virulence factors have been identified among *Cryptosporidium parvum* and *Cryptosporidium hominis* mainly related to aspects of host-pathogen interactions from adhesion and locomotion to invasion and proliferation [4].

The relationship among host factors such as age and gender and the status of the immune system with genotypic and phenotypic characteristics of the parasite define two crucial outcomes: a) virulence (the ability of a microorganism to cause disease) and b) pathogenicity (the ability of a pathogen to inflict damage to the host). Recognized virulence factors are toxins, fimbriae, flagella, and hypervariable surface proteins that play an important role in

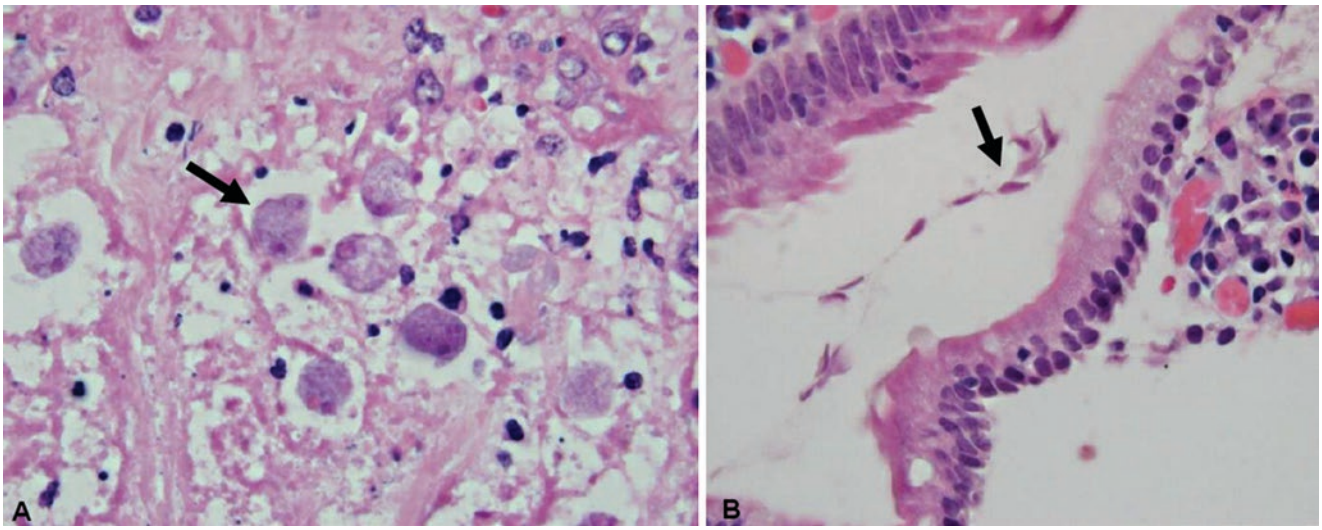

Fig. 28.2 Amoebas are large, single-cell (unicellular) microorganisms *(arrows)* with an oval-shaped nucleus (**a**). *Giardia intestinalis* light microscopy 40× (**b**). Hematoxylin and eosin stain. (Courtesy of Alejandro Velez, MD, Pathology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

adhesion, cell invasion, and resistance to the host immune response, intracellular survival, and nutrient uptake.

Cryptosporidiosis recognized as a major waterborne worldwide parasitic infection was first described in 1976 in patients with severe watery diarrhea. This parasitic infection was subsequently recognized in HIV/AIDS patients with T-cell counts less than 50 as a debilitating disease, characterized by profuse and prolonged diarrhea with abdominal pain [5].

Clinical manifestations frequently include nausea, vomiting, low-grade fever, arthralgia of weight-bearing joints, myalgia, weakness, malaise with a duration of 2–3 weeks, and self-limiting disease in immunocompetent hosts. However, sometimes it could be a life-threatening infection with biliary tract, lung, and pancreatic involvement.

Giardia intestinalis (*G. lamblia, G. duodenalis*)

It is a protozoan amitochondrial, binucleated, flagellated microorganism responsible for the most common persistent diarrhea worldwide. In a recent report from the Centers for Disease Control and Prevention of the United States, between 2011 and 2012, about giardiasis surveillance including 44 states, 16,868 (2011) and 15,223 (2012) cases of giardiasis were reported (98.8% of them confirmed) and associated with a detected outbreak. The incidence rates were 6.4 and 5.8 per 100,000 population (2011 and 2012, respectively). Cases were most frequently reported in children aged 1–4 years, followed by those aged 5–9 years and adults between 45 and 49 years. Northwest states were more often affected, and the highest peak incidence was observed during early summer through early fall [6] (see Fig. 28.2).

As occur with other parasitic infections, gastrointestinal manifestations are more often seen: vomiting, watering diarrhea, general malaise, colic, and abdominal writhing. Joint pain seldom occurs and when it occurs affects large weight-bearing joints such as the knees and ankles, and it manifests mainly as reactive arthritis (RA) [7].

Painter et al. [8] recently described the association between giardiasis and subsequent development of arthritis or joint pain in a retrospective cohort in the United States comparing people with giardiasis ($n = 3301$) vs. healthy controls ($n = 14{,}612$) matched on age and sex using a logistic regression model to evaluate for musculoskeletal manifestations in the 6 months following giardiasis infection. Joint pain or arthritis was reported 51% more often in giardiasis patients (OR, 1.51; 95% CI, 1.26–1.80) in all age groups and genders as compared with persons without giardiasis. These findings provide epidemiological support for the association between giardiasis and arthritis and also support the notion that further investigation is needed to elucidate the mechanisms involved.

Plasmodium spp.

Alphonse Laveran (1845–1922) identified *Plasmodium* as the agent of malaria. More than 175 species of *Plasmodium* have been reported since then; however, just five of them cause malaria in humans: *Plasmodium falciparum* (main cause of morbidity-mortality), *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium knowlesi* (limited to Asia). They are transmitted by the bite of an infected female mosquito (*Anopheles*). Most of them occur to persons who travel to endemic areas. Moreover, malaria could be

acquired by exposure to infected blood products, laboratory exposure, local mosquito-borne transmission, or congenital transmission.

Plasmodium infection remains a major global health issue with high morbidity-mortality rates and a high economic burden worldwide. Recent malaria surveillance in the United States, 2015, published 1517 confirmed cases, including one congenital case. *Plasmodium falciparum* 67%, *Plasmodium vivax* 11%, *Plasmodium ovale* 4%, and *Plasmodium malariae* 3% were reported. Malaria was acquired from visiting friends or relatives in the majority of afflicted people (68%). Among them, 32 women were pregnant, 23 cases were reported in US military personnel, 17% of all cases were classified as severe illnesses, and 11 patients died. The number of cases decreased by 24% (208) from 2014 to 2015. Among regions of high prevalence such as Africa, West Africa, Central and South America, and Oceania, only West Africa has shown significantly fewer imported cases [9].

Malaria shows a wide clinical spectrum and could be the cause of fever of unknown origin, and a high index of suspicion is mandatory to establish diagnosis. The clinical spectrum includes fever, chills and sweating, headache, generalized musculoskeletal pain, myalgia, cough, vomiting, and diarrhea. *P. falciparum* and *P. vivax* exhibit similar clinical pictures with complicated malaria, signs like jaundice, cough, shortness of breath, dyspnea, cyanosis, hyperemesis, hyperpyrexia, liver or spleen enlargement (so-called tropical splenomegaly), bleeding, or neurological and mental status changes which are key to establish diagnosis.

Toxoplasma spp.

This flagellate parasite was first identified in 1908 and is believed to infect up to a third of the worldwide population, described independently by Charles Jules Nicolle (1866–1936), Louis Herbert Manceaux (1865–1934) based in Tunisia, and Alfonso Splendore (1871–1953) positioned in Brazil. Samuel Taylor Darling (1872–1925) detected Sarcosporidia in a human muscle tissue removal.

Toxoplasma gondii is an obligate intracellular flagellate parasite with a great ability to invade host cells because of an exclusive actin-based motility mechanism. Toxoplasmosis means clinical manifestations due to *T. gondii* infection. It is a zoonosis, and cats and six feline species are definitive hosts, and they can transmit the parasite by different ways to humans and other warm-blooded animals. Infection may also occur by the following:

- Ingestion of food or water contaminated by cat feces
- Consumption of meat containing toxoplasma cysts (mainly undercooked seafood, pork, lamb, or deer)
- Hand to mouth from knives or tools with meat or unwashed vegetables or fruits or after gardening or cleaning a cat waste box contaminated with infected cat feces
- Intake of unpasteurized milk, chiefly goat's milk
- Placental transmission

Acute toxoplasmosis in an immunocompetent adult is often asymptomatic or sometimes a self-limiting febrile illness and influenza-like, with swollen lymph nodes, headaches, myalgia (skeletal muscle compromise), arthralgia, fever, and fatigue. However, immunocompromised patient infection can be a true emergency with central nervous system involvement (headache, confusion, seizures, coordination disorders, encephalitis, and even schizophrenia, bipolar illness, and suicidal ideas) and pulmonary symptoms (tuberculosis or *Pneumocystis*-like, cough, fever, shortness of breath, and hypoxemia). Every year, nearly 5000 persons develop visual loss by retinochoroiditis related to ocular toxoplasmosis, most acquired congenitally [10].

Infected patients with HIV/AIDS, rheumatoid arthritis patients, or patients on biologic drugs such as TNF inhibitors, high doses of glucocorticoids or DMARDs, chemotherapies, or solid organ or stem cell transplantation are particularly at high risk [11] (Fig. 28.3).

Trypanosoma spp.

The name was taken from the Greek roots *trypano-* (borer) and *soma* (body) describing how the parasite infects host cells (corkscrew-like). Nearly 30 species of *Trypanosoma* have been reported, and most of them were named according to the host they infect (e.g., *T. avium* causing trypanosomia-

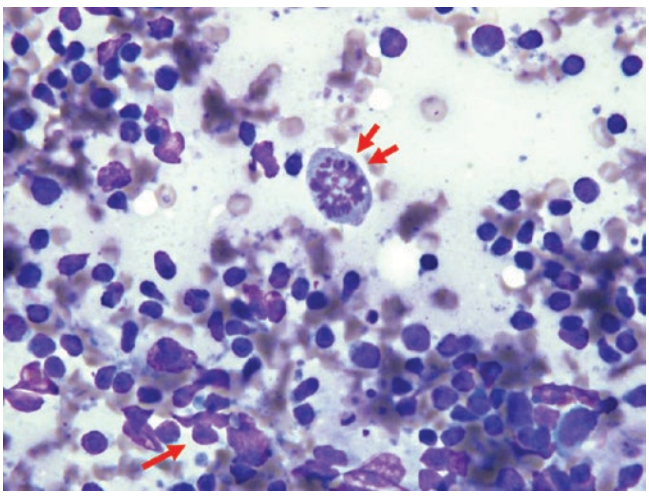

Fig. 28.3 Toxoplasma. Bradyzoites within tissue cyst *(double arrow)* and tachyzoites *(single arrow).* (Courtesy of Alejandro Velez, MD, Pathology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

sis in birds, *T. equinum* affecting horses, *T. percae* in fishes). Two species are important in humans: *T. cruzi*, a protozoan parasite responsible for Chagas disease, and *Trypanosoma brucei*, the cause of sleeping sickness, both potentially life-threatening diseases in some endemic regions (Africa; North, Central, and South America) [12].

The parasite is mainly transmitted through a vector by means of blood-feeding invertebrates (triatomine or kissing bugs) and, congenitally, through organ transplantation or blood transfusion. Most patients are asymptomatic or manifest flu-like symptoms in the acute period (2–4 weeks) with malaise, fever, arthralgia of large bones, or myalgia. Sometimes, it is easy to identify the bug bite on the skin. Immunocompromised patients and children could develop myocarditis or meningoencephalitis. Untreated patients during chronic periods may develop visceral involvement in up to 30% with heart, gastrointestinal, spleen, liver, or urinary bladder life-threatening infections.

In the United States, a recent Chagas disease surveillance report (2017) from Arizona, Arkansas, Louisiana, Mississippi, Tennessee, and Texas from blood donor centers with the objective of identifying the source of transmission was published [13]. Canine infection was not related to human spread. Different to Latin America where poorly built housing assemblies in some rural and tropical areas (e.g., cow dung mixed with mud in structural walls, palm roof) and domestic reservoirs such as dogs are high sources of transmission, in the United States, those risk factors are minor; however, 2300 infected blood donors were reported, and an estimated 63 to 315 congenital infections by *Trypanosoma* occur yearly. These data underestimate the real prevalence of infection because not everybody is a blood donor, but this is a call of attention to improve routine prenatal or newborn screening as well as to frequent travelers to endemic countries.

Helminthe Infection

Helminthes are large parasites with complex cylindrical structures and were named according to their body shape.

Trematodes

They are also known as blood flukes. Trematoda comes from the Greek *trimatodis* which means with suction cups or opening.

Schistosoma spp.

Bilharziasis or schistosomiasis (snail fever) affects approximately 200 million persons worldwide, and an estimated 300,000 deaths occur yearly. Infection is considered also an NTD mainly in the Middle East, Latin America, Southeast Asia, and sub-Saharan Africa.

Infection could originate where unprocessed human waste is used as fertilizer or compost. Five species infect humans: *Schistosoma mansoni* and *S. intercalatum* produce intestinal involvement and *Schistosoma haematobium* urinary involvement, while *Schistosoma japonicum* and *Schistosoma mekongi* are frequent in Asian populations. Most patients are asymptomatic; however, abdominal spasms, cough (bronchospasm), diarrhea, fever, urticarial skin rash, fatigue, liver and spleen enlargement, muscle aches, and eosinophilia in acute phase named Katayama fever can occur.

Urinary infection may result in hematuria, fibrosis which can lead to obstruction, and hydronephrosis with kidney failure and increased bladder cancer. Central nervous system involvement is most frequent in Asia by *Schistosoma japonicum*, with seizures secondary to granulomatous lesions in the brain or eggs in the spinal cord manifested by transverse myelitis or paraplegia [14].

A recent report from Madagascar where *Schistosoma haematobium* and *Schistosoma mansoni* are prevalent, as high as 31% and in some areas 70% of Malagasy population, described oligoarthritis. Schistosomal arthropathy is rare; but recurrent mono- or oligoarthritis of the lower limbs, mainly knees and ankles, in endemic areas could be seen [15].

Cestodes (Tapeworms)

Among cestodes, we have *Echinococcus granulosus* and *Taenia* spp.

Echinococcus granulosus

Echinococcus granulosus is a commensal parasite that resides in the small intestine of dogs (definite host) or dingos, wolves, sheep, horses, cattle, goats, and camels (intermediate host) and has been related to reactive arthritis, usually after gastrointestinal infestation in the clinical spectrum of the disease. Considered a neglected parasite disease, the adult parasite size nearly 5 millimeters has four suction cups on its scolex and a rostellum with 30–36 double-row hooks. Most dogs are infected because they feed with viscera or giblets of infected sheep, the main source of protein in some rural areas. Humans are infected by ingestion of eggs from contaminated food releasing infectious embryos that are disseminated by the bloodstream to the lungs or liver. No human-to-human transmission has been reported [16].

Hydatid cyst or echinococcosis has been reported worldwide but is endemic in Africa, South America, southern regions of the Middle East, New Zealand, Australia, India, Turkey, and Southern Europe.

Clinical symptoms could be delayed until 20 years after contagion and vary according to number, size, location, and type of cyst which can be spherical, unique, and thick walled affecting the liver (55–70%), lungs (18–35%), kidney (10–15%), spleen (5–10%), or seldom muscle-bone-

joint (1–2%) where the femur, pelvic-iliac bone, humerus, and vertebrae are most affected. Most patients complain of abdominal pain in the right hypochondrium with fever, pruritus, cough, and sometimes hemoptysis related to cyst rupture [17] (Fig. 28.4).

Taenia spp.

Taenia solium, solitary tapeworm of humans, cause taeniasis; and porcine cysticercosis has been reported as a neglected tropical disease by the World Health Organization (WHO). It is considered a top cause of death by foodborne parasite

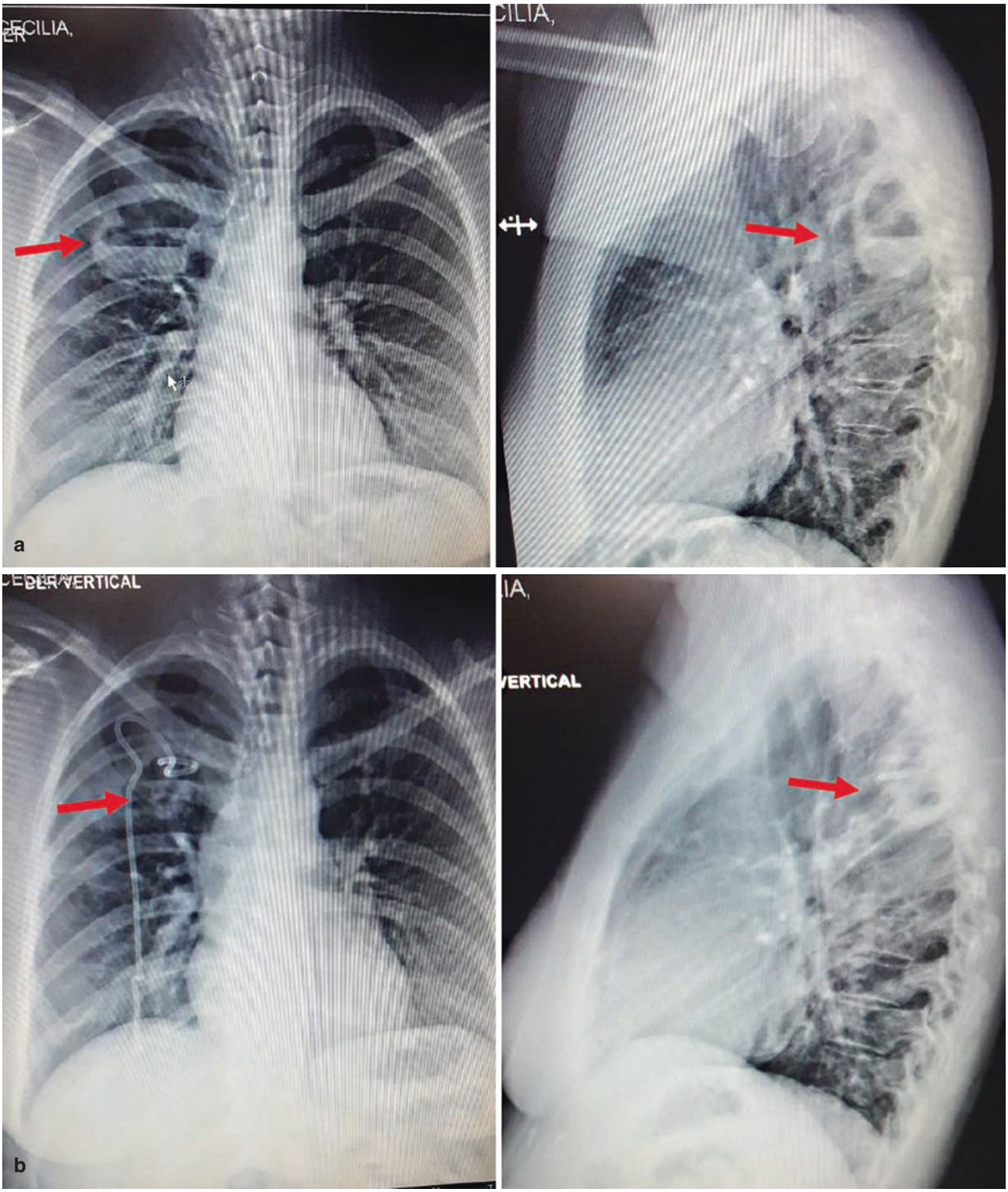

Fig. 28.4 Chest radiograph PA and lateral view showing lung hydatid cyst *(arrows)* in the superior aspect of the right upper lobe. Before (**a**) and after treatment (**b**)

worldwide. Nearly 100 species have been reported; and its name is derived from Greek *tainia* meaning ribbon, bandage, or stripe [18].

Taeniasis infection is a consequence of drinking contaminated water, ingesting contaminated raw or undercooked pork meat, or transmitting eggs to the mouth with dirty hands as occurs in children. As soon as the larva named *Cysticercus cellulosae* reaches the small intestine, the scolex (head) adheres to the intestinal wall by means of hooks and suckers until maturity, then changing to proglottids. In contrast, *Taenia saginata* (cows, beef) has no armed scolex, while *Taenia solium* has an armed scolex, which helps to differentiate both species.

Many proglottids (hundreds of them) conform the strobila (mature form which can measure 2–4 meters). Nearly 8 weeks later, gravid proglottids are ejected in the stool with an average of 50,000–80,000 fertile eggs. Pigs can then ingest contaminated stool; and larvae can lodge in fat, muscle, and the brain where they become cysts 10 to 12 weeks later completing the life cycle. Most pigs are asymptomatic because they are sacrificed and sent to meat stores for human consumption [19].

Human infection is completely different, and an estimated 50,000 deaths occur yearly worldwide due to neurocysticercosis. Thirty percent of patients complain of epilepsy, brain cancer-like, severe headache, weakness, and motor dysfunction according to location and severity of infection. All of the above are signs that may lead you to suspect the infection in endemic areas. Muscle involvement could be asymptomatic and seldom cause myalgia [20, 21].

Nematodes

Nematodes are a diverse group of parasites also named roundworms because of their shape. Nematode parasites include *Strongyloides* spp., *Dracunculus* spp. (guinea worm), and filaria spp. (*Loa loa*).

Strongyloides spp.

Strongyloides stercoralis is a parasite endemic to wet tropical and subtropical areas but also reported in the Appalachian Region of Southern United States and Northern Canada. Prevalence rate is difficult to establish because infection could appear decades after exposure and most persons are asymptomatic. However, an estimate of 100 million persons are infected globally.

Strongyloides was first described in 1876 by Luis Normand (St. Mandrier Hospital, Toulon, France) from soldiers coming from Vietnam (formerly Cochinchina). It is the one nematode which has a particularity to be able to reproduce inside humans. At least 50 *Strongyloides* species have been reported; but just two of them can infect humans, *S. stercoralis* and *S. fuelleborni*, the latter seen in African primates and humans from Oceania.

Also considered a neglected tropical disease, *Strongyloides stercoralis* hyperinfection syndrome is an emerging disease, because of a lack of awareness among health-care professionals in non-endemic areas. The infection is acquired most of the time by walking barefoot helping to penetrate the filariform larvae through the skin causing an inflammatory reaction sometimes unnoticed (papule, erythema, or edema) or significant pruritus with urticarial reaction. Occasionally, indurated trajectories can be visualized in the skin of the abdomen, thorax, buttocks, or limbs (*larva currens*) which can disappear in hours or days. Larvae reach the bloodstream and are inserted to the lungs or any organs [22].

Clinical manifestations range from asymptomatic (50%) to death by severe uncontrolled disseminated infestation (hyperinfection syndrome) with mortality rates that are approximately 43% in an immunocompetent host and 85% in immunocompromised patients.

Lung involvement can result in pneumonitis (Löffler syndrome) manifested by nocturnal cough, hoarseness, pharyngitis, gastroesophageal reflux, sometimes mild hemoptysis, and eosinophilia because of allergic reaction due to larva locomotion through the lungs.

Gastrointestinal involvement is characterized by abdominal cramps, nausea, vomiting, intermittent diarrhea, and spontaneous migration of the larvae by mouth or anus (it explains anal pruritus often seen). Sometimes weight loss, intestinal obstruction, pancreatitis, and gastrointestinal bleeding due to duodenal or colon (pseudomembranous colitis) involvement can be seen [23] (Fig. 28.5).

Musculoskeletal involvement has been reported as reactive arthritis with fever, sclerotic or uvea inflammation, and lower limb involvement [24, 25].

Risk factors to develop the most feared manifestation hyperinfection syndrome which can lead to fatal multi-organic

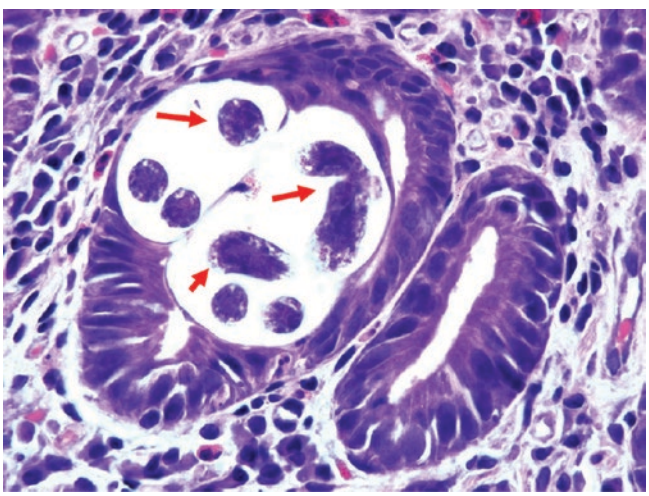

Fig. 28.5 Histopathological sample of intestinal mucosa demonstrates inflammatory infiltrate, and some fragments contain *Strongyloides stercoralis* parasites *(arrows)*. (Courtesy of Alejandro Velez, MD, Pathology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

dissemination of the parasite are high-dose glucocorticoids, chemotherapy, immunocompromised states such as malnutrition, TB, human T-lymphotropic virus type 1 (HTLV-1) or HIV infection, COPD, diabetes, malignancies, SLE, alcoholism, and nephropathy; and some with TNF inhibitor use has been reported. For all above reasons, screening for strongyloidiasis should be obligatory in HTLV-1 and HIV patients as well as transplant recipients and donors in high-prevalence areas [26].

Dracunculus spp. (Guinea Worm)

The Dracunculidae family includes two genera: *Dracunculus* (infect tissues and serous cavities of mammals, fish, reptiles, amphibians) and *Avioserpens* (affecting birds). *Dracunculus* comprise 14 species, most of which affect snakes. Adult forms are large filiform pale yellow parasites with marked dimorphism where male size is 16–40 mm, while females are larger with lengths up to 100 cm. Both have an atrophied intestine and a mouth surrounded by several papillae and a thick peribuccal ring. *Dracunculus medinensis* (guinea worm) is the causal agent of dracunculiasis, a characteristic nodular lesion in the skin of humans [27].

Considerable efforts toward eradication or to reduce the number of countries with endemic transmission which occurs when persons drink contaminated water with parasite infested by water fleas (copepods) which carry infective *Dracunculus medinensis* larvae are being carried out. In 2017, just 30 human cases were reported, all of them from Africa, Chad, and Ethiopia in contrast to 20 countries in 1980 according to WHO [28].

Clinical manifestations are seldom fatal or life-threating, follow an insidious course, and take 10–14 months until a mature maggot emerges from the body from a typical nodular lesion mainly localized in the lower limbs. Other complaints include pain present in the subcutaneous tissues with burning sensation (so-called the fiery serpent), fever, eosinophilia, malaise, and fatigue. The removal of the worm usually is done slowly, applying pressure to pull it out of the wound and wrapping the worm around a piece of gauze or small stick. Topical antibiotics should be applied to prevent secondary infection.

Filaria (*Loa loa*)

It is believed that filariasis has been present in humans since ancient times. However, the first descriptions in 1866 are attributed to Timothy Lewis and Otto Henry Wucherer who found the relationship between filariasis and elephantiasis. Finally, the adult form of the worm was described in 1876 by Joseph Bancroft and Patrick Manson who reported the parasite life cycle through mosquitoes in 1877.

Filariasis is considered another neglected tropical disease (NTD) in London (2012) and is endemic in Africa, Asia, and Central and South America where more than 120 million persons could be at risk. Filariasis is one of the six infectious diseases classified as eradicable by WHO.

There are three types of filarial worms: (1) *Wuchereria bancrofti* (more than 90% of cases), (2) *Brugia malayi* (7–8% of cases), and (3) *Brugia timori* (less than 1% of cases).

Lymphatic filariasis is the most dreaded complication, and it occurs when filaria reaches the lymphatic vessels awakening an allergic and inflammatory reaction that occludes the normal circulation. The mosquitoes involved in transmission of the parasites are *Culex* in urban areas, *Anopheles* in rural zones, and *Aedes* in some Pacific islands. After exposure to infected mosquitoes, mature forms of parasite larvae are deposited on the skin and can enter the body. The larvae will migrate to the lymphatic vessels where they develop into adult worms and can live for 10 to 15 years. Female worms discharge several microfilariae into the blood, making it possible to infect other mosquitoes by ingesting blood from an infected host repeating the cycle [29] (Fig. 28.6).

Most patients are asymptomatic which contributes to transmission of the infection. Lymphatic involvement leads to lymphedema or elephantiasis (edema and thickening of the skin and underlying tissues) on the limbs, but also affects the kidneys, genitals (scrotum or vulvar lymphedema), breast, and immune system with progressive and indolent corporal deformities. Filariasis often leads to social stigma and mental health alterations (depression), which makes it difficult to do or apply for a regular job for reasons related to social isolation and poverty with a high socioeconomic burden for any health system [30].

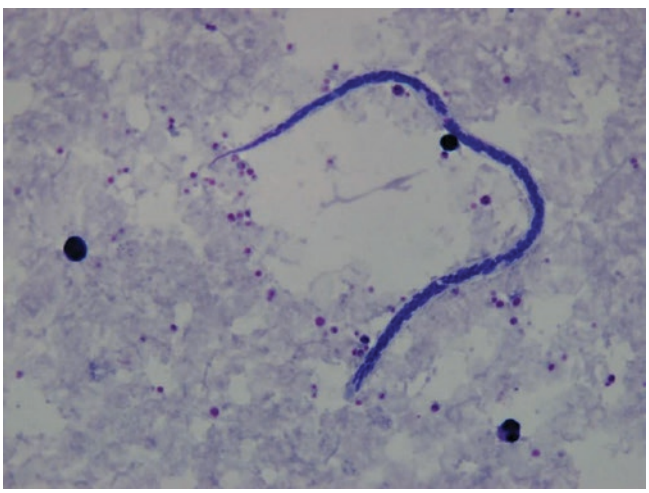

Fig. 28.6 Microscopic view of microfilariae. A roundworm nematode responsible for lymphatic filariasis. (Courtesy of Alejandro Velez, MD, Pathology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

Sometimes the Mazzotti skin reaction could help to establish the diagnosis in suspicious situations. The Mazzotti reaction is an allergic reaction with intense itching induced 1–3 hours after administration of diethylcarbamazine 50 mg to 100 mg. The reaction can be life-threatening and is characterized by fever, urticarial rash, abdominal pain, tachycardia, hypotension, arthralgia, and swollen and tender lymph nodes and occurs within a week of treatment. The reaction may correlate with intensity of infection.

Diagnosis

The diagnosis of parasitic arthritis can be difficult to establish but should be ruled out in endemic areas. Clinical picture is usually atypical with or without constitutional complaints including fever, malaise, arthralgia predominantly in the lower limbs, lack of response to conventional treatment with NSAIDs or corticosteroids, gastrointestinal involvement (abdominal pain, diarrhea), skin rash, persistent cough or bronchospasm, high C reactive protein levels as well as high erythrocyte sedimentation rate (ESR), leukocytosis, and eosinophilia which are clues to establish a diagnosis. Dramatic effectiveness to parasitic treatment helps to confirm diagnostic suspicion [31, 32].

Sometimes symptoms are bizarre and may mimic reactive arthritis, rheumatoid arthritis, SLE, septic arthritis, or early-onset spondyloarthritis. Synovial fluid may be difficult to obtain, but when available it is inflammatory in nature (more than 2000 white blood cells but less than 50.000 and less than 80% neutrophils), and parasites are not visible in the articular fluid [33, 34].

Radiological manifestations of parasitic infection may be key to establish a diagnosis (Figs. 28.7 and 28.8). Pathognomonic clues in the case of *Dracunculiasis* are helpful because sometimes the adult dead worm affects joints leading to arthritis and muscles undergoing calcification seen as a long, string-like, serpiginous appearance (curvilinear calcification of the guinea worms) in the lower limbs by plain x-rays. Differential diagnosis includes other parasites such as filarial worms (*Loa loa*) and *Onchocerca volvulus* which may show calcification but are much smaller and always seen in the hands and feet. Cysticercosis has multiple rice grain calcifications oriented toward the muscle fibers which made it easy to distinguish from *Dracunculus medinensis* [35].

Parasites should be identified; and it is mandatory to establish a specific treatment, which could be done by meticulous examination under microscopy with appropriate staining of stool sample, duodenal fluid test, urine test, muscle or skin biopsy, or immunologic-serologic tests.

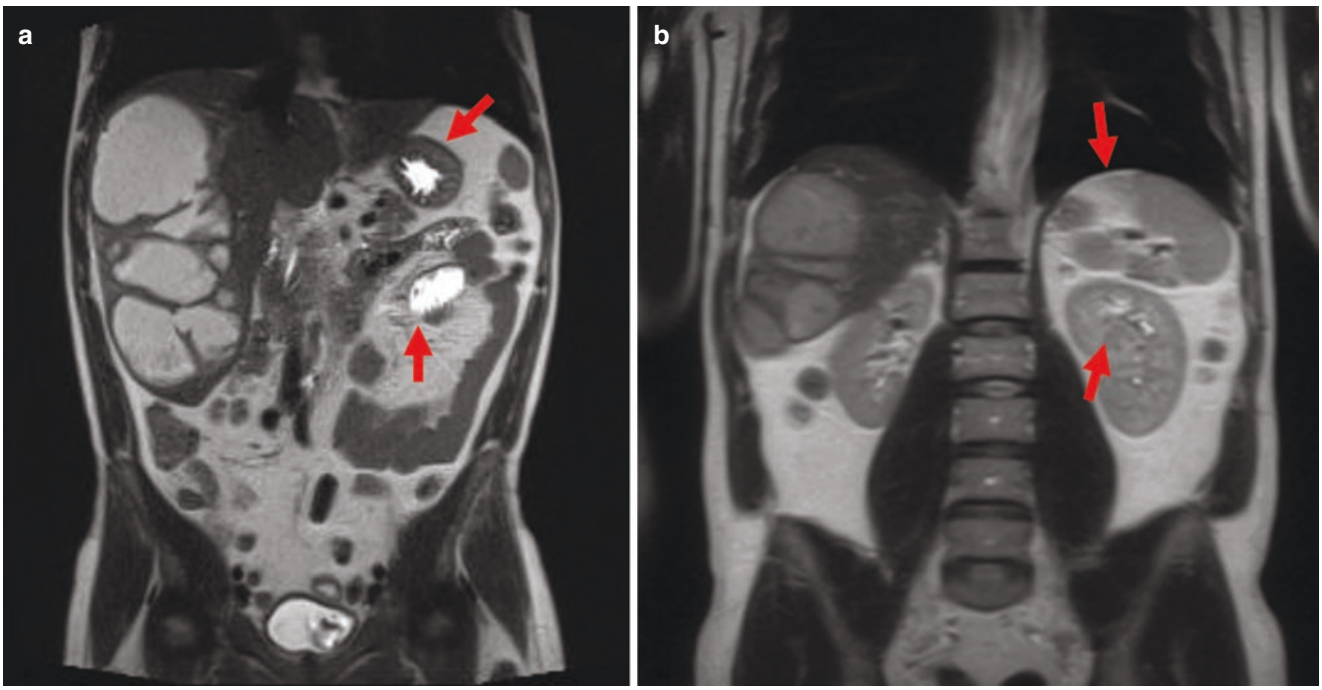

Fig. 28.7 Abdominal MR images showing hydatid cysts *(arrows)* filled with stroma in the left hypochondrium before (**a**) and after successful treatment (**b**). (Courtesy of Sergio Alvarez, MD, chief of Radiology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

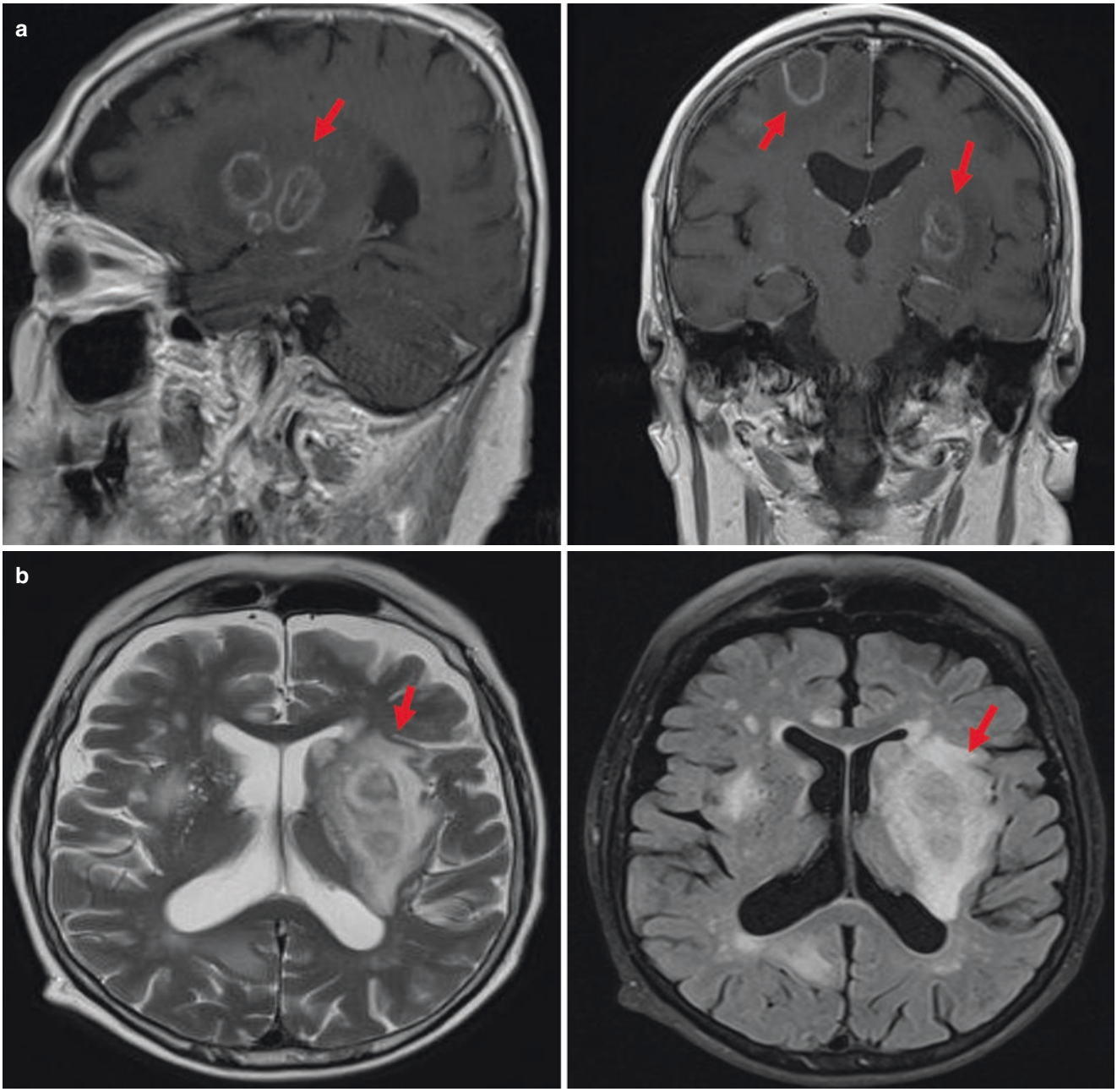

Fig. 28.8 Cerebral toxoplasmosis. (**a**) Sagittal MR images showing multiple hyperintense lesions of different sizes *(arrows)* with noticeable surrounding vasogenic edema. (**b**) Axial MR images demonstrated ring-like lesions with eccentric nodules "the target sign" *(arrows)*. (Courtesy of Luis German Pulgarin, MD, Radiology Department, Hospital Pablo Tobon Uribe, Médellin, Colombia)

Sometimes parasites are found as an incidental finding in colonoscopy, upper tract endoscopy, or bronchoscopy, even in radiological imaging studies. Synovial membrane biopsy seldom shows eggs or parasite, and it is not necessary to establish a diagnosis [36].

In 1975, Doury proposed the following criteria for the diagnosis of parasitic rheumatism:

1. Clinical features of monoarthropathy, pauciarthropathy, or polyarthropathies of an inflammatory type
2. History of a stay in an endemic parasitic country
3. No radiologic changes
4. Synovial fluid of an inflammatory type but with no parasites apparent by microscopic examination
5. Raised ESR

6. Blood hypereosinophilia
7. Direct or indirect identification of parasites in blood, urine, stool, choleric fluid, etc.
8. Total inefficacy of antirheumatic treatment
9. Great efficacy of specific antiparasitic treatment [37]

Treatment and Future Directions

The main basis for treatment is not pharmacological medications or vaccines but lies in education and hygiene measures in endemic areas [38]. Various measures, many of them of common sense, are necessary to prevent the spread of parasites. Local health authorities and international organizations (WHO, PHO) have specific recommendations for locals and travelers to endemic areas such as the following:

- Do not eat food in poor condition or with unpleasant smell or taste.
- Cook well ground meat, ground poultry, and pork to at least 175 F degrees (>80 C degrees); avoid eating raw or undercooked oysters, clams, or mussels.
- Always thoroughly peel and wash foods that are eaten raw, such as vegetables or fruits, with potable water and if it is possible a drop of chloride per liter of water used.
- Wash dishes and tools that have touched raw meat with hot water and soap.
- Use chloride and ozone filters, or boil water before consumption.
- Keep food refrigerated (as needed) to delay spoilage.
- Only drink pasteurized milk or fruit juices.
- Avoid swallowing water while swimming in rivers, seas, or pools.
- When traveling to other countries, always consume potable bottled water.
- Avoid the consumption of water of unknown origin, such as from springs.
- Stay indoors in well-screened areas, mostly at night to avoid mosquito bites; use bed nets and spray it with insect-repellant permethrin as well as wear clothes that cover most of the body.

Knowledge about new insights of how most parasitic infections evade our immune system allows new treatments, and it is necessary because we are still far away from eradication and/or cure of parasitic infections. Of interest, auranofin, an old medication used in rheumatoid arthritis, is ten times more potent than metronidazole to inhibit *Entamoeba histolytica* and *Giardia lamblia*; and it targets thioredoxin reductase stopping the reduction of thioredoxin and enhancing sensitivity of parasite to reactive oxygen-mediated killing and decreasing parasitic numbers in liver abscess or colitis [39–41].

New indications for statins and clofazimine to treat *Cryptosporidium* as well as promissory target alternatives such as bumped kinase inhibitor of *Cryptosporidium* calcium-dependent protein kinase 1, inhibitors of *Plasmodium* lipid kinase PI(4)K8 of *Cryptosporidium*, and a new inhibitor product named MMV665917 demonstrated efficacy to stop growing, reduce oocyst flaking, and diminish diarrhea in vitro and in vivo in animals with very few side effects in persons [42, 43].

Recently, a group of investigators found that plasmepsin inhibitor 49c impedes malarial egress and invasion because it targets plasmepsins IX and X in the blood, stopping these aspartic proteases indispensable to do incursion in red cell membranes of the host. New tools open a window in those resisting cases to conventional antimalarial agents worldwide as well as new advances about the role of regulatory B-cells (Breg) which play an important protective role in autoimmune conditions such as allergy, rheumatoid arthritis, SLE, and MS with deleterious effect in some individuals where profile Th1 and/or Th17 plays a pro-inflammatory role. In addition, therapeutic inhibition of Breg cells has favorable effects in cancer and bacterial and viral infections. Protozoan infections mainly malaria, toxoplasmosis, and leishmaniasis are related to this B-cell subtype by means of anti-inflammatory IL-10 production responsible for parasite-host equilibrium necessary for the chronicity and may be evaluated to target as a third-generation vaccine in the future [44, 45].

In addition, better understanding of the detoxification system of *Trypanosoma cruzi* has taken over an important role to an antioxidant enzyme named cytosolic tryparedoxin peroxidase (c/TXNPx) which is related to catalyze hydroxyperoxides and peroxynitrites. It converts *Trypanosoma* resistant to oxidative defenses of the host which is crucial to improve parasite survival and could be a future target. It is very important as an alternative to conventional drugs such as nifurtimox and benznidazole which are effective in acute disease and not in chronic stages besides deleterious effects such as hypersensitivity reactions, peripheral polyneuropathy, and bone marrow depression [46, 47].

Parasitic infection such as filariasis has shown promising response with treatment strategies like preventive chemotherapy distributed through mass drug administration (MDA strategy), but to be successful, this program must achieve a coverage of at least 80% of the population at risk with treatment annually over 5–6 years in endemic areas [48, 49].

Table 28.1 Protozoan diagnosis and treatment

Agent	Diagnostic tool	Musculoskeletal involvement	Treatment
Entamoeba histolytica	Cyst or trophozoite identification in repeated stool samples. Antibodies in serum or DNA detection by PCR	Reactive arthritis of the lower limbs	Metronidazole 250 mg–500 mg po tid for 8–10 days
Cryptosporidium spp.	Oocyst detection in stool samples with modified Ziehl-Neelsen stain. Visualization with immunofluorescence microscopy or PCR	Arthralgia of weight-bearing joints, myalgia, and weakness	Trimethoprim sulfa 160 mg/800 mg po bid for 7–14 days, nitazoxanide 500 mg bid for 3 days
Giardia spp.	Oval cyst or axostyle identification by microscopy, IFI, direct immunofluorescence. Samples from duodenal aspirate	Polyarthralgias of the lower limbs. Reactive arthritis-like	Metronidazole 250 mg–500 mg po tid for 8–10 days, tinidazole, nitazoxanide 500 mg bid for 3 days
Plasmodium spp.	Blood smear on a microscope slide. Giemsa stain is gold standard	Osteomuscular pain, myalgias, RA-like	Chloroquine[a] 600 mg at once and then 300 mg at 6, 24, and 48 hours, atovaquone 1 g plus proguanil 400 mg[a] full-strength tablets once a day for 3 days, artemether-lumefantrine, mefloquine
Toxoplasma spp.	IgG/IgM antibody detection, ELISA, indirect fluorescence antibody assay, Sabin-Feldman dye test, latex agglutination test	Myalgias (skeletal muscle compromise), arthralgia, fever, and fatigue	Pyrimethamine-sulfadoxine 3 tablets po qd for 2–4 weeks Clindamycin 600 mg po tid for 2 weeks Spiramycin 1 g qd for 3 months[a]
Trypanosoma spp.	Card agglutination test for trypanosomiasis, ELISA, latex agglutination, stained thin or thick blood smear with Wright or Giemsa stain	Arthralgia of large bones or myalgia	Pentamidine 4 mg/kg IM or IV for 7–10 days, suramin 20 mg/kg IV (baseline and days 3, 7, 14, and 21), benznidazole 2.5–3.5 mg/kg po bid for 60 days

[a]Can be used in pregnancy

Table 28.2 Trematodes diagnosis and treatment

Agent	Diagnostic tool	Musculoskeletal involvement	Treatment
Schistosoma spp.	Microscopic examination of excreta (stool, urine) is the gold standard; serological tests can diagnose less advanced infections. Rectal biopsy	Mono- or oligoarthritis recurrent of the lower limbs	Praziquantel 60 mg/kg in three doses over 1 day

Table 28.3 Cestodes diagnosis and treatment

Agent	Diagnostic tool	Musculoskeletal involvement	Treatment
Echinococcus granulosus	X rays, CT or MRI images. Detection of eggs and proglottids in feces. ELISA	Cyst in the muscle-bone-joint. The femur, pelvic-iliac bone, humerus, and vertebrae are most affected	Albendazole and praziquantel PAIR[a] Surgical cyst removal
Taenia spp.	X-rays, CT or MRI images. Detection of eggs and proglottids in excreta. ELISA for coproantigen detection. PCR-based assay	Weight loss, abdominal pain, weakness, headache by intracranial hypertension, or epilepsy if CNS[b] is compromised	Albendazole (15 mg/kg qd for 8 days) and praziquantel (5–10 mg/kg) or Niclosamide 2 g single dose

[a]PAIR puncture, aspiration, injection of protoscolicidal agent, and reaspiration
[b]CNS central nervous system

Treatment should be individualized with most patient complaints ranging from asymptomatic or mild symptoms requiring just antiparasitic agents and NSAIDs which are the treatments of choice to severe involvement requiring a multidisciplinary management approach involving multiple medical specialties including nurses, public health officials, and rehabilitation and plastic surgery specialists. A recent meta-analysis to treat echinococcosis showed that combinations of pharmacological drugs and surgery or puncture, aspiration, injection of protoscolicidal agent, and reaspiration (PAIR) was more likely to result in cure and demonstrated better outcome which could be applicable as a treatment strategy to other selected parasitic infections [50]. Specific treatment with most usual dosage of antiparasitic agents is shown in Tables 28.1, 28.2, 28.3, and 28.4.

Prognosis

Prognosis and response to treatment is usually good. Most of the time, dramatic improvement is seen as soon as specific antiparasitic treatment is initiated. However, response is related to severity of the involvement, evolution and time of symptoms, associated comorbidities, as well as immunological state of the host.

Table 28.4 Nematodes diagnosis and treatment

Agent	Diagnostic tool	Musculoskeletal involvement	Treatment
Strongyloides spp.	Larva identification in stool by (Ritchie) concentration technique. Larvae cultured with charcoal, Harada-Mori filter paper, or blood agar	Reactive arthritis of the lower limbs, urticarial skin reaction	Albendazole 400 mg po qd for 2 days or ivermectin 200 mcg/kg qd for 2 days
Dracunculus spp.	No serological test available. Identification of the white filamentous worm when appears in the skin ulcer. X-rays	Typical painful nodular lesion mainly located in the lower limbs, X-rays (curvilinear calcification)	Metronidazole 250 mg–500 mg po tid for 8–10 days or mebendazole, slow manual worm extraction, and sometimes antibiotics for skin ulceration
Filaria spp.	Microfilarial identification in blood smear collection preferably at night. Thick drop (Knott method) Wright or Giemsa stain. ELISA	Lymphedema or elephantiasis on the limbs, but also affect the kidneys and genitals	Diethylcarbamazine 2 mg/kg po tid for 12 days or 6 mg/kg in a single dose plus ivermectin 0.2 mg to 0.4 mg/kg once a year

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Whipple Disease

29

Juan D. Cañete and Julio Ramírez García

Introduction

George H. Whipple first described Whipple disease (WD) as an intestinal lipodystrophy resulting from disturbed fat metabolism in 1907 [1], and a bacterial cause was suspected only after a successful response to antibiotics in 1952 [2]. *Tropheryma whipplei*, a gram-positive actinomycete, was detected by polymerase chain reaction (PCR) in 1992 and cultured in 2000 [3]. The *T. whipplei* genome contains a relatively small number of genes associated with energy metabolism, suggesting it is dependent on its host to acquire specific substrates for energy metabolism in the intracellular vacuoles of macrophages [4, 5].

Thanks to the detection of *T. whipplei* by specific PCR and antibodies [6], it is known that chronic asymptomatic carriage of *T. whipplei* is common, as it has been detected in stool and saliva in around 2–11% of the general population, and may reach 26% in sewage workers and 37% in relatives of WD patients; Senegal has a higher prevalence of asymptomatic carriers of *T. whipplei* [7, 8]. Currently, humans are the only known host for *T. whipplei*, and all environmental sources are related to humans and their wastes. Asymptomatic carriers of *T. whipplei* represent a large reservoir from which other humans might be colonized. Oral-oral and fecal-oral transmission are the main routes [9, 10].

Classic WD (CWD) is a rare chronic condition affecting multiple organs with a late onset (mean age at onset 55 years), which affects $1/10^6$ individuals, mainly white males. WD is fatal if left untreated, and relapses occur in 2–33% of treated cases, even after prolonged appropriate antibiotic treatment. The clinical manifestations of CWD are intermittent arthralgia/arthritis, diarrhea, abdominal pain, and weight loss. However, about 25% of WD patients present only cardiac or neurological manifestations without companion gastrointestinal or articular symptoms [11].

WD may be diagnosed by duodenal biopsy in most cases. Histological detection of foamy macrophages containing large amounts of diastase-resistant periodic acid-Schiff (PAS)-positive particles in the lamina propria of the duodenum, gastric antral region, jejunum, or ileum is the standard diagnostic method. For a definitive diagnosis, confirmation by PCR is recommended [3].

Due to the reported natural resistance of *T. whipplei* to trimethoprim and sulfonamides in vitro, treatment with doxycycline and hydroxychloroquine is currently recommended to prevent relapses [12].

Microbiology

T. whipplei is a rod-shaped, gram-positive bacterium that was cultured for the first time in 1997. Based on the ribosomal DNA sequences, *T. whipplei* belongs to the actinomycetes, a group that also contains other known pathogens, such as *Nocardia*, *Rhodococcus*, *Mycobacterium*, and *Corynebacterium* spp. [13].

The *T. whipplei* genome contains a relatively small number of genes associated with energy metabolism; the bacterium is dependent on its host to acquire specific substrates for energy metabolism. Therefore, its culture requires a living eukaryotic host cell due to the lack of specific metabolic pathways [4, 5]. The development of a synthetic medium that contains amino acids and other essential components that *T. whipplei* is unable to synthetize was successfully used to culture the bacterium in the absence of cells [14]. Although the specific axenic medium has allowed the culture and the establishment of several strains of *T. whipplei*, its very long doubling time (up to 18 days) severely hampers the diagnostic utility of routine culture [13].

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_29

The digestive lumen is the probable site of multiplication of *T. whipplei*, where it is phagocyted and ineffectively degraded in macrophages. *T. whipplei* replicates within mucosal macrophages and peripheral blood mononuclear cells. Recent evidence indicates that *T. whipplei* is a commensal organism and not an obligate pathogen [11].

The bacillus of *T. whipplei* has been found in sewage water, other water sources, and soil. In humans, it has been found to occur at a higher percentage in sewage plant workers (up to 26%). In addition, *T. whipplei* has been found in duodenal samples, in saliva, and in human feces (up to 4% in Europeans) of asymptomatic people [6–8]. Although spores have not yet been identified, *T. whipplei* possesses regulatory factors essential for sporulation, which might facilitate survival in the environment, as human beings are the only known host [5]. Seventy-two different genotypes of *T. whipplei* among 191 positive samples from patients have been reported. Although genetic variations within *T. whipplei* might contribute to disease manifestation, thus far, no clear relationship between genotype and clinical symptoms has been reported [13].

Epidemiology

Classic Whipple disease (CWD) is a rare condition, as indirect evidence points to a prevalence of 1 per 1 million people and an annual incidence of between 1 and 6 per 10 million people. CWD typically affects Caucasian males (around 96%) between 50 and 60 years of age, with a mean of age of onset of joint symptoms of 40.3 years [15]. The bacterium was found only in duodenal biopsy specimens until the introduction of PCR. Since then, *T. whipplei* has been detectable in almost all biological human samples. Asymptomatic carriers of *T. whipplei* represent a large reservoir from which other humans might be colonized. Oral-oral and fecal-oral transmission are the main routes.

The gut is the preferred niche, and the bacterial load in stools is higher than in saliva samples. Symptomatic patients have significantly a higher content of *T. whipplei* in fecal samples than asymptomatic carriers, indicating that a high load of *T. whipplei* is associated with symptomatic infection [15].

Sewage and surface water have been shown to contain *T. whipplei*-specific DNA and are thus a possible environmental source of infection. Farmers and individuals exposed to animals may be at the highest risk, although studies in various kinds of animals did not detect *T. whipplei*. The seroprevalence for specific antibodies against *T. whipplei* in the general population varies from 50% in France to 70% in Senegal [16, 17]. At least 75% of infected individuals clear primary *T. whipplei* infections, but a minority (<25%) become asymptomatic carriers, of whom very small proportion develop WD (<0.01%). Infection is therefore necessary, but not sufficient, for WD; and it is unclear whether prolonged asymptomatic carriage necessarily precedes the disease [6].

Pathogenesis

The discrepancy in the ubiquitous environmental occurrence of *T. whipplei*, the rarity of the disease, and the existence of long-term asymptomatic carriers, cases of recurrent infections, and familial cases, as well as the lack of association between *T. whipplei* genotypes and clinical manifestations, suggest that host genetic factors contribute to the development of the disease [18]. However, WD patients are not prone to other severe infections [13], and WD has never been reported in patients with conventional primary immune deficiencies [19].

A recent study in a French family, in which four members had WD and several others were asymptomatic carriers of *T. whipplei*, shows that heterozygosity for the R98W allele of IRF4 is the genetic etiology of WD in this kindred. The mutation causes a loss of function of IRF4, which is a transcription factor involved in the immune response. Although the authors found no IRF4 mutations in a pilot cohort of 25 patients with sporadic WD, they suggest that these and other patients may also develop WD due to other inborn errors of immunity, possibly related to IRF4, as suggested by the apparent genetic heterogeneity and physiological homogeneity underlying severe infectious diseases [20]. Other genetic associations with WD have been reported: HLA alleles DRB1∗13 and DQB1∗06 and IL-16 polymorphisms [11].

The pathological hallmark of WD is a massive accumulation of macrophages infected by *T. whipplei* in the duodenal mucosa, which are alternatively activated through *T. whipplei*-induced IL-16 expression, which upregulates Th2 cytokines (IL-10, IL-4) and downregulates Th1 cytokines (IL-12, IFNg) conferring tolerogenic properties to dendritic cells and impairing the elimination of the microbe. The Th2 environment promotes the replication of *T. whipplei* and its dissemination by induction of macrophage apoptosis [21].

A recent study has shown that *T. whipplei* increases the expression of human leukocyte antigen-G (HLA-G) on monocytes. HLA-G is a non-classic HLA molecule with immunotolerogenic activity that has been involved in transplantation, cancer, and immune-mediated inflammatory diseases. HLA-G expression inhibits the expression of proinflammatory cytokines such as TNF, resulting in reduced macrophage bactericidal activity and bacterial replication. The study suggests that increased HLA-G expression in patients with WD results from the intracellular persistence of *T. whipplei* and confers an immune privilege that creates a protected niche for bacterial replication [18]. In line with these findings, TNFi administered to patients with

undifferentiated/seronegative arthritis due to occult *T. whipplei* infection accelerates the transition to classic systemic WD [22].

Taken together, recent studies suggest that susceptibility to *T. whipple*i infection is associated to mutations in genes that code for transcription factors involved in the immune response, such as IRF4. Finally, infected macrophages are switched from pro-inflammatory to anti-inflammatory profile of cytokines, creating the proper environmental conditions for *T. whipplei* growth and replication.

Clinical Manifestations

The clinical spectrum of *T. whipplei* infection encompasses the classic systemic form, predominantly involving joints and the intestinal tract, with diarrhea and weight loss; localized forms (arthritis, uveitis, central nervous system (CNS) disease, and endocarditis) without involvement of the intestinal tract; acute, self-limiting infections such as acute gastroenteritis, acute pneumonia, or bacteremia; and asymptomatic carriers, who are more prevalent than expected [3, 11].

Joint Manifestations

As joint manifestations are the initial symptoms in 75% of cases of WD, many months or even years before the beginning of gastrointestinal symptoms, it is important for rheumatologists to understand how to diagnose and handle them properly to prevent progression to systemic disease. Most patients have intermittent migratory joint symptoms with either oligoarthritis or polyarthritis. Arthritis is slightly more common than arthralgia (41–62% and 26–54% of cases, respectively) and usually involves the large joints (knees, ankles, wrist, elbows, shoulders) in an asymmetrical pattern [23]. The joints are normal between flares, but increased serum C-reactive protein (CRP) levels reflect chronic systemic inflammation. Therefore, unexplained intermittent oligoarthritis or polyarthritis of the large joints in a middle-aged man should suggest WD, even in the absence of gastrointestinal manifestations [23].

Gastrointestinal involvement is demonstrated by histological or PCR tests in the vast majority of cases. A few patients, however, have chronic focal joint infection with normal gastrointestinal tests [24].

The initial intermittent joint pattern becomes continuous but without either joint destruction or rheumatoid factor. Joint space narrowing at the carpal, carpometacarpal, radiocarpal, and hip joints has been reported in a few patients with prolonged untreated WD. Axial involvement is less common and often is associated with peripheral arthritis [24].

In our department, the six patients finally diagnosed with CWD over 30 years were Caucasian males, with a mean age of 56 years, all of whom debuted with joint symptoms: four with intermittent arthritis (oriented as palindromic rheumatism), one with polyarthritis and fever (initially oriented as adult Still's disease), and one with migratory arthralgia (initially oriented as possible lymphoma). The range of time from the onset of joint symptoms to the onset of digestive symptoms (which determined the final diagnosis in five out of six patients) was 63–120 months. All patients presented weight loss and had abdominal lymphadenopathy. Fever was reported in three patients. One patient had sacroiliac involvement and carpal erosion, but none were RF or HLA-B27 positive [25].

The last patient diagnosed with WD was referred to our department in 2015, after 10 years of asymmetric intermittent arthritis with intermediate uveitis and RF, ACPA, and HLA-B27 negativity. The patient had not been treated with conventional synthetic or biological DMARDs. A right knee arthroscopy with synovial biopsy was performed due to the suspicion of WD, which was confirmed by PAS-diastase staining and PCR positivity in the synovial membrane. Although there were no previous or current abdominal symptoms, gastrointestinal involvement was confirmed by PCR and PAS-positive jejunal biopsy. Two weeks later, the patient was admitted to the emergency room due to acute dyspnea and oxygen desaturation. Chest X-ray revealed alveolar edema and left pleural effusion. Transesophageal echocardiography detected aortic insufficiency without vegetations. Blood cultures were repeatedly negative, and the patient underwent aortic valve replacement surgery. The pericardium and aortic valve tissue were positive for *T. whipplei* (PCR and PAS+ staining) (Fig. 29.1). Although the patient had only poor language fluency and cerebral MRI was normal, cerebrospinal fluid was *T. whipplei* positive on PCR. The patient was treated with IV meropenem and daptomycin for 14 days, followed by trimethoprim-sulfamethoxazole and hydroxychloroquine for 12 months. All *T. whipplei*-related symptoms improved, without relapse. This case highlights the importance of a systematic diagnostic workup in patients with suspected WD, taking cardiac and cerebral involvement into account.

Several atypical forms of WD presenting with rheumatic symptoms have been reported, such as seropositive polyarthritis treated with DMARDs diagnosed as WD after emergency valve replacement surgery positive for *T. whipplei* 4 years later or subacute inflammatory low back pain resulting from L2–L3 discitis diagnosed after *T. whipplei*-positive PCR from the disk lesion [26].

Given the severity of WD, the infection should be considered in middle-aged men with seronegative intermittent joint symptoms with an atypical course and with persistent systemic inflammation (high CRP) despite treatment. As biological therapy may aggravate the disease, *T. whipplei* infection must be ruled out before starting biological treatment or when symptoms appear reflecting organ involvement in patients with biological therapy for atypical arthritis [22]. *T. whipplei* infection should also be excluded in patients

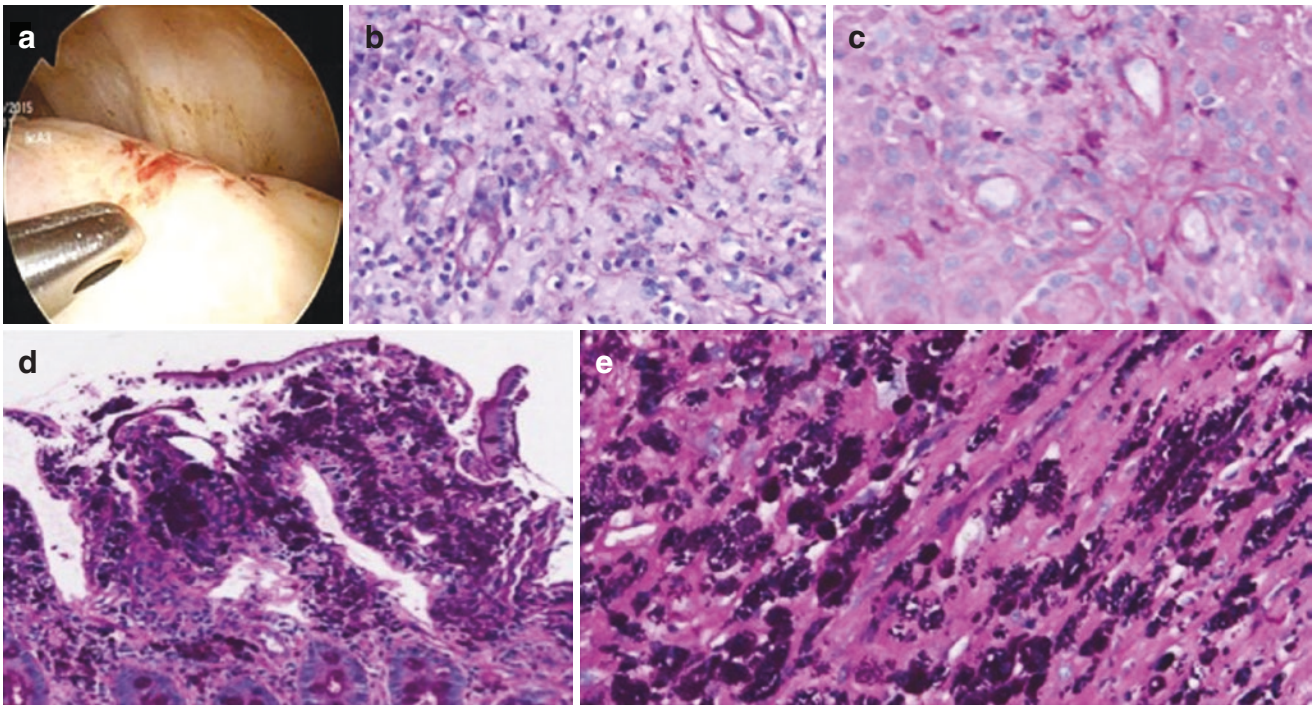

Fig. 29.1 Synovial, jejunal, and aortic valve tissue biopsies in a 52-year-old man with CWD. (**a**) Right knee joint arthroscopy showing a subpatellar view of the synovial membrane, which is edematous with patchy erythematous appearance, before obtaining the synovial tissue for diagnostic purposes. (**b**) Synovial membrane stained with periodic acid-Schiff (PAS) showing infiltrate with PAS-positive macrophages (magenta colored), ×20. (**c**) The same synovial membrane with PAS-diastase staining highlighting pink particles within macrophages, ×20. (**d**) PAS staining of jejunal biopsy of the same patient showing lamina propria infiltrate of macrophages containing PAS+ particles, ×20. (**e**) Aortic valve tissue from the same patient showing the characteristic macrophage infiltrate containing PAS+ particles, ×20

with seronegative intermittent arthritis with improvement in joint symptoms after antibiotic treatment for concomitant mild infections (pharyngotonsillitis, bronchitis, urinary tract infections).

Clinical Manifestations Which Should Suggest Infection by *T. whipplei* [15]

- Unexplained intermittent arthritis with persistently high C-reactive protein
- Atypical arthritis which improves after antibiotic treatment for concomitant infections
- Chronic asymmetric polyarthritis affecting mainly large joints and negative for RF and ACPA antibodies
- Chronic diarrhea
- Prolonged fever of unknown origin
- Unexplained neurological manifestations
- Uveitis
- Endocarditis with negative blood cultures
- Development of extraarticular manifestations (gastrointestinal, cardiac, or neurological symptoms or fever) in a patient receiving biological therapy for polyarthritis

Localized Forms of *T. Whipplei* Infection

Chronic *T. whipplei* infections located in organs without histological intestinal and systemic involvement have been described. Localized infections have not systemic involvement, and the potential for relapse is not the same as in classic WD, suggesting a different susceptibility to *T. whipplei* between patients with localized and systemic WD [27].

A variable proportion of patients have CNS involvement, the most serious complication of WD, which often has a bad prognosis. Headache and cognitive dysfunction are possible symptoms of CNS involvement, but are not diagnostically useful due to the lack of specificity. The triad of dementia, supranuclear ophthalmoplegia, and myoclonus is considered highly specific for WD and should raise clinical suspicion. Supranuclear ophthalmoplegia, oculomasticatory myorhythmia, and oculo-facio-skeletal myorhythmia are pathognomonic for WD. Epilepsy, ataxia, seizures, insomnia, and meningitic symptoms or peripheral nerve and spinal cord involvement are nonspecific. *T. whipplei* is detected in cerebrospinal fluid in 50% of patients, most of whom do not have CNS symptoms [28, 29]. If the correct diagnosis is established early in the course of WD, long-term antibiotic therapy can result in effective long-term cure. However, recovery from a severe neurological deficit may not occur [28].

Ocular involvement (uveitis) is reported in up to 11% of patients [3] and may be unilateral or bilateral and posterior, intermediate, and/or anterior; and it is characterized by chronicity and resistance to corticosteroids [29]. Uveitis in the context of arthritis could lead to a wrong diagnosis of spondyloarthritis.

T. whipplei endocarditis mainly occurs among 60-year-old afebrile Caucasian men with cardiac insufficiency or embolic events. In a series of patients with chronic *T. whipplei* infections, 11% presented with endocarditis without classic WD. Cardiac involvement, when present, is principally detected by cardiac murmurs and signs of heart failure, with negative blood culture, often requiring surgical replacement of the mitral or aortic valve [27, 29].

Lung involvement is not uncommon. Pulmonary infiltration and pleural effusion are reported in 40–50% of WD patients, some of whom show no clinical or histological signs of gastrointestinal involvement. In a series of 142 patients with *T. whipplei* infection, 24 (17%) had localized infection with no gut involvement [30].

Localized *T. whipplei* infection should be considered in the case of neurological symptoms in the CNS or unexplained isolated joint involvement or when adenopathy, pulmonary, or pleural involvement or uveitis cannot be ascribed to other causes. *T. whipplei* infection is also the most frequent agent identified in isolated culture-negative endocarditis. In these localized infections, WD can only be identified by histological or PCR analysis of affected extraintestinal organs [11, 26].

In recent years, *T. whipplei* has been reported to cause both chronic disease with various symptoms and acute symptomatic infections presenting as acute gastroenteritis. *T. whipplei* was detected in 15% of feces from hospitalized diarrheic 2- to 4-year-old children. As well, there is data supporting association of *T. whipplei* with adult traveler's diarrhea [29]. This bacterium has also been detected in 3% of bronchoalveolar lavage (BAL) samples collected in intensive care units, also was cultured from BAL of a patient with pneumonia, and was involved in lung complications associated with HIV infection [31]. *T. whipplei* has been detected in 6.4% of blood specimens from febrile patients without malaria in Senegal, suggesting that it may be associated with fever [29].

Diagnosis

The most common routine diagnostic methods are histopathology and PCR, which are available in most laboratories, while culture of *T. whipplei* remains difficult and is limited to fewer centers.

WD may be diagnosed from duodenal biopsies in most cases. Although gastrointestinal symptoms are sparse or lacking in some patients, duodenal histology is positive in most patients. Negative PAS staining does not definitely rule out WD, but substantially reduces the probability [11].

PAS-positive histology with foamy macrophages may also be observed in patients with other bacterial infections, including *Rhodococcus equi*, *Mycobacterium avium-intracellulare*, *Corynebacterium*, *Bacillus cereus*, *Histoplasma*, or fungi. Ziehl-Neelsen staining differentiates non-acid-fast *T. whipplei* from acid-fast mycobacteria.

If WD is clinically suspected, multiple biopsies should be taken from diverse duodenal sites due to the often patchy distribution of the bacterium. Newer endoscopic techniques (e.g., capsule endoscopy, virtual chromoendoscopy) may also be helpful [11, 13].

T. whipplei-specific immunohistochemistry has been used since the availability of specific *T. whipplei* antibodies. Immunohistochemistry is now an important diagnostic procedure that can be applied to almost all patient samples and detects *T. whipplei* before the typical PAS-positive foamy macrophages appear. It is also helpful for the differentiation from atypical mycobacteriosis, for the discrimination of unspecific PAS staining in CNS or colon biopsies, and for monitoring patients on therapy to ascertain histological remission in cases of doubt [32].

Although *T. whipplei* western blot serology has been proposed to complement positive PCR results in stools or saliva to discriminate between asymptomatic *T. whipplei* carriage and WD, approaches to a serological diagnosis of WD have, so far, not become generally applicable [13].

PCR is increasingly used to diagnose WD, as it is believed to be more specific and sensitive than other methods. PCR results are reliable if confirmed by sequencing or multiple *T. whipplei* target genes or both, to avoid false positives. Analysis of the duodenal mucosa may be negative in localized (isolated) chronic infections with *T. whipplei*. In these cases, samples from clinically affected sites should be assessed as PAS-positive cells may be detected from any other infected solid organ, followed by PCR analysis to confirm *T. whipplei* infection. PCR is of exceptional diagnostic value in patients who have received immunosuppressive therapy and for samples from sterile body fluids such as cerebrospinal fluid, synovial fluid, ascites, and pleural effusion and from CNS biopsies [3, 11, 13].

Samples in contact with the environment (e.g., stomach, small bowel, and lung) may be PCR positive (despite PAS negativity), a finding not usually sufficient for the diagnosis of WD. However, PAS staining of samples from the colon, rectum, or CNS or biopsies from the eyes may also be nonspecific and do not definitively indicate WD, but should be confirmed by techniques such as PCR or immunohistochemistry [13].

Contamination, the main risk of PCR techniques, may occur during various steps of the PCR process, including sample collection and DNA isolation, and during PCR amplifications. In atypical cases of *T. whipplei*, two specific target genes should be tested, and the results of both should be positive in order to rule out potential false-positive results [13].

Recent studies have suggested that detection of *T. whipplei* by PCR in urine has added a new noninvasive sample to the repertoire of diagnostic tests for WD. Urine samples were positive in 9 out of 12 cases of WD, but negative in controls, including those carrying *T. whipplei* in feces but without illness. The authors concluded that this test can be helpful in diagnosing WD [33, 34], as the detection of *T. whipplei* DNA in urine may be useful in the diagnosis of localized infections, the detection of relapses, ruling out *T. whipplei* infection before starting biological therapy in cases of atypical arthritis, and the diagnosis of isolated acute infections. Therefore, this new technique could play a major role in the understanding of the spectrum of *T. whipplei* infections [34].

Treatment

WD may be fatal without appropriate treatment, although exact mortality rates are unknown. Although antibiotic treatment of *T. whipplei* infections usually leads to rapid clinical improvement, eradication requires prolonged treatment. Symptoms such as diarrhea, joint pain, and fever usually disappear within a week, while other symptoms may take several weeks to disappear. It is difficult to cure patients with late symptoms such as eye, heart, and CNS involvement; and these patients tend to have high relapse and mortality rates [3, 11, 13, 29].

For whatever reason, it is commonly believed that there are frequent late relapses after antibiotic treatment. The utility of supplementing antibiotic therapy with IFNg to enhance the antibacterial effects may be effective in overcoming antibiotic resistance and/or relapses [3, 11].

Until now, there has been no noninvasive method of monitoring patients, making it difficult to evaluate the effectiveness of therapy; but, as commented previously, detection of *T. whipplei* in urine by PCR could become a reliable, noninvasive method of monitoring the response to antibiotics [33, 34].

Antibiotics

Several antibiotic combinations have been used since 1952, including penicillin, streptomycin, tetracycline, ceftriaxone, meropenem, cotrimoxazole, doxycycline, and hydroxychloroquine. All studies have included relatively small groups of patients, and there are no larger studies. Furthermore, relapses were not uncommon in patients receiving these antibiotics [13].

Currently, the recommended treatment is based on a single randomized controlled trial in which 40 patients were successfully treated with ceftriaxone (1 dose of 2 g/day) or meropenem (3 doses of 1 g/day) for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months [35]. In patients intolerant to ceftriaxone, meropenem may be an alternative; and in cotrimoxazole-intolerant patients, doxycycline can be used [11, 13].

Whole-genome sequence analysis and the successful culturing of *T. whipplei* permitted sequence-based analysis and in vitro susceptibility testing, which led to discussion of the effectiveness of the first-choice regimen, as in vitro data suggest an intrinsic resistance of *T. whipplei* to trimethoprim, which was confirmed by sequence analysis showing that the target for trimethoprim (dihydrofolate reductase) is missing. In addition, mutations in the gene encoding dihydropteroate synthase (*folP*), the target of sulfonamide, were reported to result in resistance to sulfamethoxazole and sulfadiazine. This hypothetical resistance was confirmed by a recent retrospective analysis in which all 14 patients who were first treated with cotrimoxazole failed treatment [12, 13]. Therefore, the replacement of Septrin and cotrimoxazole by alternative antibiotics may be indicated.

A more rational alternative to ceftriaxone followed by cotrimoxazole is the combined use of hydroxychloroquine and doxycycline, because hydroxychloroquine increases intravacuolar pH and decreases *T. whipplei* viability, as vacuole acidification is critical to the survival of the bacterium in phagosomes. The combination of the two compounds is the only treatment that is bactericidal against *T. whipplei* in vitro [29].

The treatment algorithm for CWD is doxycycline (200 mg/day) and hydroxychloroquine (600 mg/day) for 12 months. For localized *T. whipplei* infection, doxycycline (200 mg/day) and hydroxychloroquine (600 mg/day) for 12–18 months, with a lifetime follow-up, is proposed. Although in vitro susceptibility data support this regimen, there is only limited in vivo evidence supporting this combination of antibiotics, with only a few prospective trials being carried out [11, 13]. Some authors recommend the classic antibiotic treatment [13].

It should be taken into account that patients receiving immunosuppressive therapy or who have immunocompromising conditions have more severe *T. whipplei* infection outcomes. In addition, WD exacerbation is associated with therapy with corticosteroids and tumor necrosis factor inhibitors, which should be avoided when possible.

Previous immunosuppressive treatment is a major risk factor for the development of immune reconstitution inflammatory syndrome (IRIS) in CWD, which is characterized by the reappearance of inflammatory symptoms, mainly fever and arthralgia, after a period of effective antibiotic treatment. It affects about 10% of treated patients, and it has been suggested that *T. whipplei* must have an immunosuppressive effect on CD4 T-cells because of the frequent emergence of IRIS after antibiotic treatment of Whipple disease.

Activated CD4 T-cells escape the peripheral blood and home onto affected tissues, causing the clinical symptoms seen in IRIS patients [13]

Correct therapy is essential in patients with IRIS which, if untreated, may be fatal. Oral corticosteroids are the first-choice treatment, and the response is normally rapid. When the inflammation does not remit within 24 h, additional or alternative immunosuppressive agents may be prescribed [11, 13].

Treatment Monitoring

Duodenal biopsy samples should normally be obtained at 6-month intervals; and therapy should continue as long as samples remain positive, although this advice may be outdated, for various reasons. Obtaining biopsy samples is costly and not without risk for complications. The procedure may be stressful. WD is known to be associated with lifetime susceptibility to *T. whipplei* infections. Macrophages can remain in the *lamina propria* for years after successful treatment, and therefore the detection of PAS-positive foamy macrophages cannot be considered as definitive evidence of incomplete bacterial remission [3, 11, 13, 29].

While PCR is more sensitive in general, PAS staining and immunohistochemistry are not influenced by the masking effect of the biofilm and are therefore more suitable for the detection of *T. whipplei* after treatment. Determination of *T. whipplei* by PCR in urine could be a noninvasive, reliable tool to monitoring the evolution of the disease in treated patients [33, 34]. Although relapse rates of WD were initially reported to be 30%, the current rates seem to be much lower. Although evidence shows that relapses can be treated successfully using the same antibiotics utilized in the initial treatment, it may be prudent to change the antibiotic regimen when relapses occur [13].

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Part IV

Reactive Arthritides

Infection and Spondyloarthritis

30

Benjamin S. Naovarat and John D. Reveille

Introduction

Reactive arthritis (ReA) refers to the constellation of articular, entheseal, mucocutaneous, and ocular symptoms that arise after a respiratory, enteric, or urologic infection. In its broad definition, ReA follows a variety of infections, bacterial, mycobacterial, viral, fungal, and parasitic (Table 30.1), and includes such diseases as Lyme disease, Whipple's disease, parvovirus B19 infection, and HIV and chikungunya infection. In this chapter, we will restrict ourselves to those associated with peripheral or axial spondyloarthritis. Other types of reactive arthritis, such as poststreptococcal ReA and Whipple's disease, are dealt with in other chapters in this textbook and will not be the focus here.

Historical Context

The development of arthritis associated with diarrheal illness was first noted by the ancient Egyptians as far back as 1200 BC [1]. Christopher Columbus was suggested as being afflicted with ReA [2]. From the American Revolutionary War, there is an interesting description of likely ReA following dysentery occurring in the setting of the unsuccessful campaign of Generals Philip Schuyler and Benedict Arnold to capture Quebec in 1775 [3]. Unfortunately, diarrhea peaked at the worst possible time, before the long and muddy portage from the Kennebec to the Chaudiere. The army's physician, 22-year-old Isaac Senter (Fig. 30.1), set up a field hospital at the "Great Carrying Place" to care for "a formidable number" of men who were too weak to proceed.

A significant but unspecified number of these soldiers also suffered from "rheumatism." Dr. Senter described one patient with the "most violent rheumatism I ever saw, not able to help himself any more than a newborn infant, every joint in his extremities inflexible and swelled to an enormous size" [3]. Brodie (Fig. 30.2) described a "classic" case of ReA in 1818: "This was a case in a man aged 45 years in 1817, presenting with urethral discharge, fever, joint swelling and inflammation of the eyes, which, as so often happens, relapsed six and nine months after the initial onset." Brodie also cited four similar cases studied by him in 1809 [4]. So years before Hans Reiter and Fiessinger and LeRoy described their first cases in 1916 [5, 6], this disease was well established. The term "reactive arthritis" was coined by Ahvonen and colleagues in 1969 [7].

The best known case of historical outbreak of ReA was after 344 Finnish patients developed ReA following the epidemic of *Shigella flexneri* dysentery in 150,000 patients in 1944 [8]. Furthermore, other well-known cases of *Shigella* dysentery have also occurred among American sailors on the USS Kitty Hawk in 1962 [9] and among Toronto policemen with an outbreak of *Salmonella typhimurium* in 1985 [10]. The largest outbreak of *Salmonella typhimurium* dysentery in the USA occurred among Chicago residents in 1985 [11] totaling over 16,000 culture-confirmed cases and was traced to two brands of pasteurized 2% milk produced by a single dairy plant. However, associated litigation has limited reports of ReA, although this author was made aware of numerous ReA cases that occurred as a result of the outbreak because of giving legal testimony in lawsuits resulting therefrom. The epidemic strain was easily identified because it had a rare antimicrobial resistance pattern and a highly unusual plasmid profile; study of stored isolates showed it had caused clusters of salmonellosis during the previous 10 months that might have been related to the same plant, suggesting that

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_30

Table 30.1 Organisms implicated in reactive arthritis

Genitourinary	Gastrointestinal	Respiratory	Others
Chlamydia trachomatis[a]	*Salmonella typhimurium*[a], *Salmonella enteritidis*[a], *Salmonella paratyphi*[a]	*Chlamydia pneumoniae*[a]	Parvovirus B19
Ureaplasma urealyticum	*Shigella flexneri*[a], *Shigella dysenteriae*[a], *Shigella sonnei*[a]	Group A beta-hemolytic streptococcus	*Brucella abortus*
Mycoplasma genitalium[a]	*Yersinia enterocolitica*[a], *Yersinia pseudotuberculosis*[a]		*Bacillus Calmette-Guerin*
Gardnerella vaginalis	*Campylobacter jejuni*[a], *E. coli*, *Campylobacter fetus*		*Chikungunya virus*
	Clostridium difficile[a]		HIV
	Giardia lamblia		*Borrelia burgdorferi*
	Tropheryma whippelii		

[a]Associated with HLA-B27

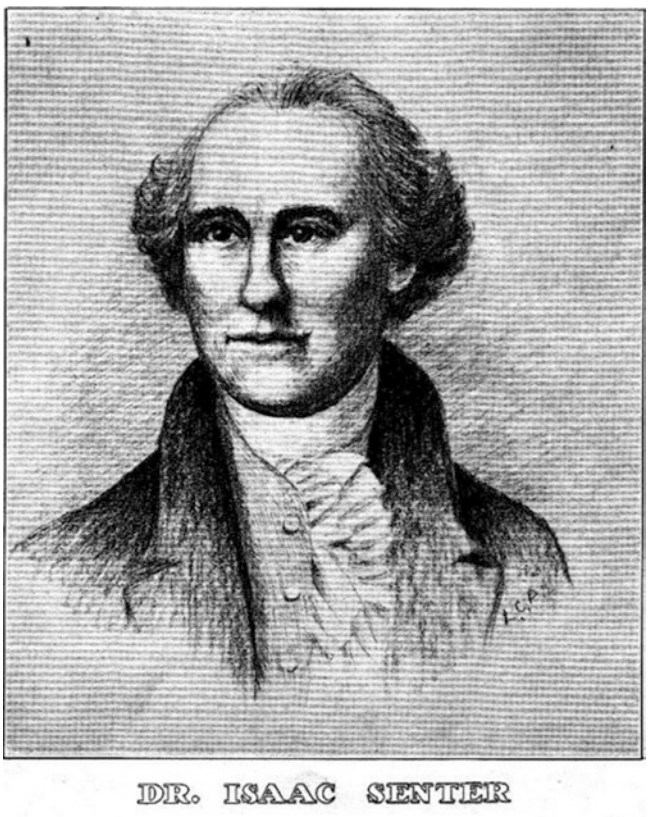

Fig. 30.1 Dr. Isaac Senter, 1755–1799. (Photo from US Army Medical Department, Office of Medical History, website. United States Government works (17 USC 403). Available at https://history.amedd.army.mil/booksdocs/rev/MedMen/MedMenIllustrations.html. Accessed on 4/29/2019)

the strain had persisted in the plant and repeatedly contaminated milk after pasteurization.

The Usual Suspects

Microorganisms implicated in ReA share common biologic features: (1) they can invade mucosal surfaces and replicate intracellularly and (2) they contain lipopolysaccharide (LPS) in their outer membrane.

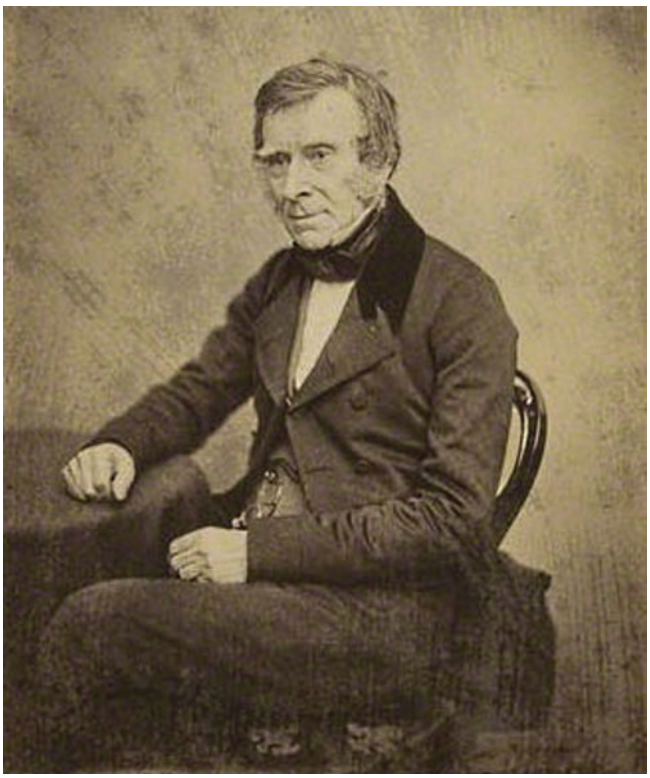

Fig. 30.2 Sir Benjamin Brodie, 1783–1862

Endemic ReA

The most frequent type of ReA in developed countries is due to urogenital infections arising from infections with *Chlamydia trachomatis* [12]. *Chlamydia* are nonmotile obligate intracellular bacteria that can infect a variety of human cell types such as muscle cells and immune cells such as macrophages and monocytes [13]. Their development cycle takes place within membrane-bound cytoplasmic inclusions that produce an infectious elementary body as well as a noninfectious reticulate body. The elementary bodies are taken up by endocytosis, while the active reticulate bodies multiply within the cell. Subsequently, the elementary bodies are then released by host cell lysis or exocytosis to propagate

infection. *Chlamydia* persists in the joint, and the active persistent *Chlamydia* demonstrates changes in gene expression and energy uptake that promote persistence within the cell. Inflammation occurs when *Chlamydia* elicits a TH1- or TH17-type immune response that recruits T-lymphocytes, TNF-α, interleukin 1, and interferon-γ. Of particular interest was the finding of *Chlamydia trachomatis* DNA in the synovial tissues and synovial fluid of patients with ReA [14] and undifferentiated spondyloarthritis [15], a finding that has been replicated elsewhere [16, 17] although lack of concordance for the findings from different laboratories studying the same samples [17, 18] and the finding of microorganisms in the joints of patients with other rheumatic diseases [17, 18] or even healthy individuals [19] underscores the need for better standardization of the procedures used for detection. Infection with *Chlamydia trachomatis* is often accompanied by coinfection with *Chlamydia pneumoniae* [18, 20], although genes of the latter are expressed at lower levels than *Chlamydia trachomatis* [21]. *Chlamydia pneumoniae* can also be a cause of ReA by itself [22]. The serovariant of *Chlamydia trachomatis* associated with ReA has been shown to be more commonly that of the ocular, as opposed to the genital type [23]. It is noteworthy that C*hlamydia trachomatis* has been found in articular tissues even during periods of clinical remission [24], although the finding of *Chlamydia* DNA levels falling [16] or even disappearing [25] with antibiotic treatment underscores that this bacterium is likely a driving force in endemic ReA pathogenesis.

ReA has also been described in patients with *Mycoplasma genitalium* urethritis, though this is much rarer than with *Chlamydia* species [26]. *Ureaplasma urealyticum* has also been implicated, though less commonly than *Chlamydia* [27]. There are also case reports of HLA-B27-associated reactive arthritis following *Gardnerella vaginalis* infections [28–30].

Postdysenteric ReA

Postdysenteric ReA, more commonly encountered in "developing countries," follows various *Shigella* and *Salmonella* species (especially *Salmonella typhimurium* and *Salmonella enteritidis*), *Campylobacter jejuni*, *Yersinia pseudotuberculosis*, and *Campylobacter fetus* and, in Europe, *Yersinia enterocolitica*. Of particular note, antigens from *Salmonella* and *Yersinia* and *Chlamydia* have been found in synovial tissues and fluids of patients with ReA, often many years after the initial infection.

Salmonella

Salmonella is probably the best studied of the postdysenteric ReA-triggering organisms. The presence of HLA-B27 has been found to modulate intracellular growth of *Salmonella*, allowing its persistence [31, 32]. One recent study showed that HLA-B27 expression can reduce the threshold of endoplasmic reticulum stress induction and HLA-B27 misfolding, and the unfolded protein response cellular environment resulting therefrom is associated with enhanced *Salmonella* replication. Moreover, *Salmonella* can induce the UPR [33]. *Salmonella* outer membrane proteins can be recognized by synovial fluid CD8 T-cells and stimulate the production of cytokines of the IL-17/IL-23 axis [34, 35]. Of note was the finding of

Salmonella, *Shigella*, *Campylobacter*, *and C. trachomatis* DNA in synovial samples of patients not only with ReA, but other types of SpA [36]. However, *Mycobacterium tuberculosis* DNA was also found in some samples, raising concerns about the specificity of this testing.

Shigella

The primary *Shigella* species associated with ReA is *Shigella flexneri*, although *Shigella dysenteriae* can also trigger ReA. *Shigella sonnei* was once thought not to be associated with ReA [37], although cases have since been reported [38]. A meta-analysis of articles encompassing 4636 patients with *Shigella* infection, of which 56 ReA cases were found, calculated a pooled incidence rate of 0.012 (95% CI 0.009–0.015) or, in other words, an incidence of 12 ReA cases per 1000 cases of *Shigella* infection [39].

Campylobacter

Campylobacter jejuni is the most common cause of human bacterial enteritis accounting for 5–14% of all diarrheal diseases worldwide [40]. An extensive review of the available literature suggested that *Campylobacter* ReA may occur in 1–5% of those infected [41]. The annual incidence of ReA after *Campylobacter* or *Shigella* may be 4.3 and 1.3, respectively, per 100,000. A population-based study of *Campylobacter*-associated ReA did not find an association with HLA-B27 [42] though it has been reported in individual patients. Other *Campylobacter* species associated with ReA include *Campylobacter coli*, *Campylobacter lari* [43], and possibly *Campylobacter fetus* [44].

Yersinia

Yersinia enterocolitica [7, 45] (predominantly of pathogenic serotypes O:3 and O:9) and *Yersinia pseudotuberculosis* [46] have both been implicated in ReA triggering, primarily in Europe, though case reports exist from elsewhere. Of note was the demonstration of *Yersinia* antigens and *Yersinia*-specific 16S ribosomal RNA (rRNA) sequences in the synovial fluid of a patient with *Yersinia* ReA [47].

The Less Well-Known Suspects

Clostridium difficile

Less commonly reported is *Clostridium difficile* as a cause of ReA [48–51]. Criteria have been proposed for *C. difficile* ReA [49], namely, (1) a sterile inflammatory arthritis with preceding diarrhea and prior antibiotic exposure, (2) stool test positive for *C. difficile* toxin, and (3) no alternative diagnosis for arthritis or diarrhea.

Giardia lamblia

Giardia lamblia-associated arthritis has been reported in individual cases [52–55]. Children seem to be affected more commonly than adults, and there is a predilection for lower extremity joints, especially the knees. The diagnosis is made by finding the organisms in the stool.

Diagnostic Methodologies to Establish the Infectious Trigger in ReA

For the clinical diagnosis of the preceding infection, serology is widely used. Unfortunately, poor standardization of the methods has affected the accuracy of associations between serologic findings and clinical presentations. A widely encompassing review focusing on several serologic techniques and their performance and limitations in the diagnosis of *Yersinia*, *Campylobacter*, *Salmonella*, *Shigella*, and *Chlamydia trachomatis* looked into this in detail [56].

ELISAs became widely used for the diagnosis of ReA in the 1990s. The tests for the diagnosis of antecedent *Chlamydia trachomatis*-triggered ReA have had widespread use; however, the evidence of specific antibodies does not prove casualty, and problems of standardization still remain unsolved, which led to the authors' conclusion that whatever serology for *C. trachomatis* is used, it is of a limited value for ReA.

Serologic documentation of *Salmonella* has evolved, and this test demonstrates antibodies to O-, H-, or Vi-antigens separately and used to support diagnosis of ReA. False-positive reactions might be common due to intrinsic cross-reactivity with malaria and enterobacteria infections. Disappointingly, also newer tests for IgM and IgG antibody detection lack sufficient sensitivity (max. 70%) and specify (max. 88%) [56]. The best way to establish a diagnosis of an acute *Chlamydia* infection is still finding a positive culture or PCR from a urine sample or urethral or vaginal swab.

Demonstration of antibodies to LPS of salmonellae other than *S. typhi* is common practice, especially in *S. typhimurium* or *S. enteritidis* infections, although these are also highly prevalent in controls; and in veterinary studies, no association was found between positive serology and bacteriology [57].

Shigella flexneri, *Shigella sonnei*, and *Shigella dysenteriae* are associated with ReA on the basis of positive culture in patients with diarrhea; and despite advanced Lumixex technology that allows simultaneous detection of specific antibodies to recombinant invasion plasmid antigens (Ipa) B, C, and D as wells as to LPS from *Shigella sonnei*, *Shigella flexneri* 2a, and *Shigella dysenteriae*, this technology has not yet been widely evaluated to support a ReA diagnosis.

Finding *Yersinia* antibodies by ELISA or immunoblot is common in the general populations of Europe, and their value in establishing a diagnosis of ReA has not been established [56].

Campylobacter serology is highly variable. There is a high prevalence of positive antibodies as people age, so diagnostic serology is more informative in younger subjects. Finding IgM antibodies determined by ELISA gives the most accurate assessment of acute infection, though there are few data to support their use in ReA.

The *Klebsiella* Saga

Although certain enteric organisms have been shown to trigger ReA, some of the most intense and controversial investigations have been in the role of *Klebsiella* in the pathogenesis of AS. This saga began in 1977, when a group in London found a significantly increased frequency of *Klebsiella* in the feces of patients with "active" disease [58], which they were able to confirm in a larger cohort the following year, even finding that a positive *Klebsiella* stool culture in a patient with inactive disease predicted a future flare [59], even showing that the presence of fecal *Klebsiella* correlated with ESR and CRP levels [60]. This was confirmed in another longitudinal study [61]. The significance of these findings was heightened over the next 2 years when a group in Australia found that HLA-B27-positive individuals with AS had a significantly lower in vitro lymphocyte responsiveness to *Klebsiella* antigens, as compared with B27-positive and B27-negative healthy controls [62], and that a rabbit antiserum to one *Klebsiella* isolate lysed the lymphocytes of B27-positive AS patients but not those of B27-positive or B27-negative controls [63]. These studies led to the idea that AS was another type of reactive arthritis.

However, within a year or two, other groups reported they were unable to confirm that fecal carriage of *Klebsiella* was either associated with disease activity in AS or predictive of future flares [64, 65], although one of these studies instead suggested that fecal carriage of *Klebsiella aerogenes* was instead associated with acute anterior uveitis [65]. The latter was strengthened by the finding of *Klebsiella* ultrasoni-

cate preparation to inhibit the binding of vitreous humor by 25–100%, compared with an inhibition of 5–30% by a similar quantity of *Escherichia coli* ultrasonicate preparation and sera from rabbits immunized with whole *Klebsiella* microorganisms or *Klebsiella* extracts to bind labelled vitreous humor antigens greater than sera from rabbits immunized with *Escherichia coli*, *Streptococcus pyogenes*, and phi X 174 virus, suggesting *Klebsiella* microorganisms may carry antigenic determinants which resemble vitreous humor antigens [66, 67].

This led to a speculation as to the mechanism by which *Klebsiella* triggered AS. The London group proposed molecular mimicry between *Klebsiella* (and other enterobacterial) capsular antigens and HLA-B27, backed by the finding of cross-reactivity between some antigens found in several gram-negative microorganisms and HLA-B27 lymphocytes [66, 68]. The Australian group isolated and characterized a *Klebsiella* K43-derived soluble cell wall factor that could render the lymphocytes of B27-positive healthy controls susceptible to lysis by anti-*Klebsiella* antiserum, implying that modification by environmental agents of specific major histocompatibility complex-associated gene products may be an important element in the pathogenesis of the HLA-B27-linked arthropathies [69].

Subsequently, studies from other centers could not confirm these findings, with no differences between the results obtained with lymphocytes from the AS patients and those with lymphocytes from the normal controls and no evidence of cross-reactivity, even in antisera with activity against both HLA-B27-positive lymphocytes and *Klebsiella* [70–72]. Similarly, other studies could not confirm the increased *Klebsiella* carriage in the stool to correlate with active AS [73–78] or AAU [79, 80].

Studies examining specific antibodies to *Klebsiella* in AS have produced conflicting results. Initial testing reported elevated IgA antibodies to *Klebsiella* in patients with active AS (but not inactive AS) compared to other rheumatic diseases or controls [81]. This gave rise to the "cross-tolerance" hypothesis, which proposes that ankylosing spondylitis is a ReA following infection by gram-negative bacteria and tissue damage is produced by antibacterial antibody binding to cross-reacting self-antigens [82]. However, a specific anti-*Klebsiella* antibody response for AS was not seen by other groups, some of whom suggesting that active AS was characterized instead by elevated IgA antibodies to various enterobacteria in both AS [83–87] and AAU [88] irrespective of HLA-B27 status, with some raising doubts about the "molecular mimicry" theory [84, 86]. However, the "molecular mimicry" was revived by the finding of homology of amino acids between HLA-B27 and *Klebsiella pneumoniae* nitrogenase, with 53% of patients with ReA and 29% of patients with AS containing antibodies to residues 69–84 of HLA-B27 compared to 5% of B27-positive controls and greater than 40% of HLA-B27 patients with AS or RS having antibodies to *Klebsiella* residues 184–193, while none of the normal nonarthritic HLA-B27 haplotype subjects did, suggesting an autoimmune response directed against HLA-B27 that was initially induced against *nitrogenase* proteins of *Klebsiella pneumoniae* [89]. This was further confirmed by immunoperoxidase staining, using antisera to synthetic peptides representing antigens shared between HLA-B27.1 and *Klebsiella pneumoniae nitrogenase* in synovial lining cells, vascular endothelium, and infiltrating inflammatory cells [90]. This was confirmed elsewhere [91], but not in subsequent studies [92, 93]. Some groups were able to find instead IgA antibodies to *Klebsiella* capsular polysaccharides [94–100] or other *Klebsiella* proteins [101–103], such as heat shock 65 or collagen [103, 104], and correlation with gut inflammation in AS [105]. Even some studies finding autoantibodies against *Klebsiella* found them also against other enterobacteria, without correlation with disease activity [106–109] or AS per se [110–113], or directed against the *Klebsiella nitrogenase* protein [106–115] or associated with cross-reactivity with HLA-B27 [116]. Other proteins cross-reactive with HLA-B27 were subsequently implicated in this "molecular mimicry" hypothesis, instead of *Klebsiella* nitrogenase, including a pullulanase protein of *Klebsiella pneumoniae* [117] and antibodies to a plasmid (pHS-2) isolated from arthritogenic *Shigella flexneri* strains [118]. One recent study reported even no distinction between AS and chronic back pain and the presence of *Klebsiella* antibodies [119].

The findings of the Australian group of the soluble *Klebsiella* "modifying" cell wall factor were confirmed by another group [120] and extended, with molecular characterization of the factor [121–125], which ultimately was found to be a feature of other enteric bacteria (*Salmonella*, *Shigella*, *E. coli*, and *Campylobacter)* [126]. The original group describing this suggested this to be a plasmid [123]. However, other groups could not confirm the presence of a "modifying cell wall factor" [127–129], and the possibility of an AS-triggering *Klebsiella* plasmid was not confirmed by another group [130]. Other groups have failed to find any evidence of *Klebsiella* (or other enteric bacteria) DNA in synovial material from patients with ReA [131], and studies of affected and unaffected family members in familial AS have demonstrated no significant differences with respect to cellular or humoral immune responses to *K. pneumoniae* and three control microbes [132].

By the middle of the last decade, the lack of any consistent compelling story implicating *Klebsiella* in AS susceptibility or severity caused the interest in further researching this topic to wane, although there is still one recent published report of *Klebsiella* protein antibody responsiveness in patients with AS persisting [133] and the popularity of "low-starch" diets [134, 135] as well as "anti-*Klebsiella*"

dietary supplements [135], with little evidence of effect on disease activity. Dr. Ebringer continues to push his *Klebsiella* hypothesis at scientific meetings, quoting the old data from his own group but not the confounding studies. Most of the SpA community has moved on from this focus, but some of its advocates remain.

Conclusion

This chapter has reviewed available evidence of the array of microorganisms implicated in susceptibility to ReA, including possible mechanisms in how these environmental factors may trigger disease. The "usual suspects" (*Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*) are well established and the rarer triggers (*Ureaplasma*, *Mycoplasma*, *Gardnerella*, *Clostridium*, *Giardia*) less so. The use of antibody testing or PCR of joint fluid or synovial tissues is complicated by lack of specificity and standardization between laboratories. The *Klebsiella* story in AS as another example of ReA has been fraught with controversy. Most of the original findings have not been widely confirmed, although some investigators continue to push this line of investigation.

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Acute Rheumatic Fever

31

Luis R. Espinoza

Acute rheumatic fever (ARF) is a systemic disease that results from an autoimmune response to infection with the group A streptococcus (GAS), *Streptococcus pyogenes* [1–3]. ARF characteristically appears 2–4 weeks following a throat infection by GAS and affects mainly a population between 3 and 15 years of age, without ethnic and/or geographic predilection and with varying degrees of inflammatory changes in the joints, heart, central nervous system (CNS), skin, and subcutaneous tissue. Worldwide, approximately 500,000 new cases of ARF occur annually, and at least 15 million people have chronic rheumatic heart disease [4–6].

ARF is the prototype of reactive arthritis, seldom life-threatening, and except for the valvular lesions usually resolves without significant sequelae. Its most dreadful complication is chronic rheumatic heart disease, which may lead to heart failure, stroke, or death [7, 8]. ARF is a disorder directly related to poor economic conditions; and its incidence has greatly diminished in developed countries, but still persists, and there is some indication that its incidence may be increasing in some less developed countries of the world [9, 10].

Epidemiology

ARF is no longer considered a public health problem in developed countries; but recurrent outbreaks, especially in developing countries and certain Southern European countries, continue to occur [11–14]. The incidence of ARF fluctuates according to socioeconomic development, but it has declined in North American and European countries over the past several decades. Most recent data suggest that its annual incidence ranges between 8 and 51 per 100,000 among children and young individuals, with lower incidences in certain parts of the world and higher incidences among indigenous people in Australia, New Zealand, and Central Asia [15, 16].

The decline in the incidence of ARF is most likely related to improved standard of living including hygiene, easier access to antibiotics and medical care, and reduced household crowding living conditions [17]. In view of the variability in global disease burden in ARF in recent years and to avoid overdiagnosis in low-incidence populations and underdiagnosis in high-risk populations, flexibility in applying diagnostic criteria in different populations at risk has been recommended. With this in mind, the following has been suggested:

(a) Consider individuals to be at low risk for ARF if they come from a population known to experience low rates of ARF or rheumatic heart disease.
(b) In the presence of reliable epidemiological data, low risk should be defined as having an ARF incidence of <2 per 100,000 school-aged children (usually 5–14 years old) per year or an all-age prevalence of RHD of <−1 per 1000 population per year.
(c) Children not clearly from a low-risk population are at moderate to high risk depending on their reference population [17–19].

Pathogenesis

The pathogenesis of ARF is complex, multifactorial, and not completely understood. However, the presence of throat infection by GAS is mandatory as well as the presence of antibodies to *Streptococcus pyogenes* [20–22].

Group A beta-hemolytic streptococcus is a bacterium composed by a capsule, cell wall membrane, cytoplasm, and nucleus. The cell wall has three layers, the outer being a protein, carbohydrates in the middle, and mucopeptides in the deep layer. The proteins M, T, and R are the most important antigenic structures and are localized in the outer portion of the cell wall and, due to their strong anti-phagocytic activ-

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_31

ity, are recognized rheumatogenic markers of the bacteria [23–25]. Protein M, abundant component of GAS, decreases the activation of the alternate pathway of the complement system leading to a reduction of polymorphonuclear-related phagocytosis. The antigenic difference exhibited by protein M allows classification of the streptococcus in more than 80 serotypes of which 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29 constitute the rheumatogenic serotypes [26–28]. The expression of these serotypes varies in the distinct geographic areas, within the same populations, and the microorganism serotype profile may vary from year to year.

The intimal mechanism of immune-mediated tissue damage in ARF is based on a latency period of about 2–4 weeks between the throat infection by GAS and onset of the clinical manifestations in a genetically predisposed host, presence of antigenic sequences or epitopes common or similar between GAS and host tissues, and high immune reactivity to antigenic components of GAS, which are different from a control population. Streptococcal antigens mediate activation of antibodies against streptococcal components, which cross-react with host proteins (molecular mimicry), resulting in immune-mediated tissue inflammation and injury [29, 30].

Molecular mimicry has been implicated as a leading hypothesis in the autoimmune-mediated pathogenesis of ARF and its complication, valvular disease [31, 32]. Potential mechanisms in which the GAS M protein might be implicated include the sharing of antigenic epitopes between GAS M protein and the carbohydrate antigen (N-acetyl-beta-D-glucosamine) and host cardiac myosin and laminin on heart valves [33]. It has also been shown that monoclonal antibodies directed against these antigens cross-react in vitro with human myosin and valvular endothelium [34]. And in addition, immunization with recombinant streptococcal protein M antigens induces autoantibody formation and valvular inflammatory changes in Lewis rats [35]. Molecular mimicry is also invoked for the adaptive immune response-induced inflammatory changes seen in ARF in which T-cell clones derived from rheumatic lesions react with myosin and valve-derived proteins with the release of inflammatory cytokines following in vitro exposure to these antigens.

Both innate and adaptive immune responses against valve proteins participate in the induction of valvular damage in ARF. Upregulation of vascular adhesion molecule 1 ensues the binding of cross-reactive antibodies on the valve surface facilitating the adherence and infiltration by mononuclear cells and release of pro-inflammatory cytokines such as interferon-γ and TNF-α, associated with decreased expression of IL-4 and IL-10 [36, 37]. Kim et al. recently analyzed the immune response to group A streptococcus in peripheral blood mononuclear cells from an aboriginal ARF cohort and found a dysregulated IL-1B-granulocyte-macrophage colony-stimulating factor (GM-CSF) cytokine axis. Persistent IL-1B production was coupled to overproduction of GM-CSF and selective expansion of CXCR3+CCR4−CCR6−CD4 T-cells, which are a major source of GM-CSF. CXCL10, a potent T-helper 1 chemoattractant, was elevated in sera of ARF patients. GM-CSF has been shown to be a key effector cytokine in autoimmune disease including myocarditis [38]. Release of other self-antigens such as vimentin and collagen leads to amplification of tissue damage [39]. The inflammatory process eventually leads to neovascularization and fibrosis, leading to valvular lesions of chronic rheumatic heart disease. It should be noted that mechanisms other than molecular mimicry might also be implicated in the pathogenesis of ARF and its complication, rheumatic heart disease [40].

ARF occurs in approximately 0.3–3% of individuals with GAS throat infection, which suggests an underlying genetic component to its development. It has also been shown that monozygotic twins have a higher risk of concordance for ARF than dizygotic twins (44% vs. 12%) and that inheritance is non-Mendelian and polygenic, with a variable and incomplete penetrance [41, 42]. Further support for a genetic component is given with the presence of rheumatic fever-associated B-cell alloantigen in the majority (92%) of patients with ARF [43, 44]. More recent published data including genome-wide association studies suggest that several polymorphisms of genes involved in both innate and adaptive immune responses may also participate in genetic predisposition to ARF [45–47].

Evidence in Support of Genetic Susceptibility to Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD)

- High risk of concordance among monozygotic twins than dizygotic twins.
- Inheritance appears to be non-Mendelian and polygenic, with variable and incomplete penetrance.
- HLA class I and II alleles:
  - HLA-B35 and HLA-B44 for rheumatic heart disease
  - HLA-DQB1∗ and HLA-DQB1∗0301 associated with a trend to risk/protection relating to ARF and the development of RHD
- Cytokine gene polymorphisms in genetic susceptibility to RHD:
  - TGF-ß1
  - IL-10
  - CTLA4
  - TNF-alpha
  - IL-1RA
  - Others: MBL2, FCN2, TLR2, FCGR2A

MLB2 mannose-binding protein, *FCN2* ficolin-2, *TLR2* toll-like receptor 2, *FCGR2A* Fc fragment of IgG low-affinity IIa receptor, *TGF-ß1* transforming growth factor-ß1, *IL-10* Interleukin-10, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *TNF-alpha* tumor necrosis factor-alpha, *IL-1RA* interleukin 1 receptor antagonist

Pathology

Fibrinoid degeneration of collagen is one of the earliest histopathologic changes observed in cardiac tissue involved in the inflammatory process in ARF. Nodules of Aschoff are virtually pathognomonic of rheumatic heart disease and are composed by epithelial cells and myocytes of Anitschkow, which are derived from histiocytic cells and macrophages [48]. Their presence is closely related to the development of progressive fibrosis and stenosis of the mitral valve. Pericarditis involves both layers of the pericardium and leads to thickening and fibrinous exudate. Rheumatic endocarditis is characterized by the presence of verrucous lesions in the periphery of valves and infiltrated by amorphous and eosinophilic material. Neovascularization with granulation and fibrous tissue occurs during the chronic phase of the process.

Synovitis is characterized by the absence of pannus formation and erosions by focal infiltration of polymorphonuclear cells and lymphocytes within the synovial and periarticular tissues. Subcutaneous nodules have a central area of necrosis, surrounded by histiocytes and fibroblasts, and lymphocytes and polymorphonuclear cells surrounded small blood vessels. Nodules and skin rash, erythema marginatum, tend to rapidly heal without scar formation.

Risk Factors

Age, especially younger age, is a predisposing risk factor for ARF. Its incidence is highest among children aged 10–14 years, followed by those aged 5–9 years. Children younger than 5 years seldom develop ARF, and a first episode is rare beyond age 30 years. Recurrences, however, can occur at older ages but are rare beyond 40 years.

Low socioeconomic conditions are one of the strong predisposing factors for developing ARF, most likely directly related to household overcrowding, which facilitates transmission of GAS.

The role of ethnicity is controversial, ARF can occur in any ethnic group, and the increased susceptibility observed in certain ethnic groups can be explained based on poverty and overcrowding, rather than genetic susceptibility.

Diagnosis

Diagnosis of ARF requires demonstration of the presence of major and minor criteria and laboratory evidence of a recent streptococcal throat infection [49].

There is no single laboratory test or clinical finding pathognomonic for a diagnosis of ARF. But diagnosis should be highly suspected in patients exhibiting certain clinical manifestations, especially fever and musculoskeletal and cardiac manifestations. It should be kept in mind that the older the individual is, the more musculoskeletal involvement will predominate, while cardiac manifestations will be seen in much younger individuals.

A precedent pharyngeal infection, 2–4 weeks prior, occurs in the majority (>75%) of patients, although GAS infection might be unapparent in over 50% of recurrent RF. Following this latency period, which may last less than a week or exceptionally more than 4 weeks, patients become symptomatic, and laboratory abnormalities might be present.

In 1944, Dr. Jones proposed a series of criteria to facilitate the diagnosis of ARF [49]. These criteria have been modified in several occasions; and the last one appeared in 2015, but always keeping in mind Dr. Jones's intentions that criteria used for diagnosis of ARF should maintain low sensitivity and high specificity, especially for low-risk populations [15, 50] (Table 31.1).

The most recent revision to the Jones criteria considers recent evidence supporting the use of Doppler echocardiography in the diagnosis of carditis as a major clinical manifestation of ARF. It also brings them into closer alignment with international guidelines for the diagnosis of ARF by defining high-risk

Table 31.1 Revised 2015 Jones criteria

A.	**For all patient populations with evidence of preceding GAS infection**	
	Diagnosis: Initial ARF	Two major manifestations or one major plus two minor manifestations
	Diagnosis: Recurrent ARF	Two major or one major and two or three minor
B.	**Major criteria**	
	Low-risk populations	*Moderate- and high-risk populations*
	Carditis[a]	Carditis
	∗Clinical and/or subclinical arthritis	∗Clinical and/or subclinical arthritis
	∗Polyarthritis only	∗Monoarthritis or polyarthritis
		∗Polyarthralgia[b]
	Chorea	Chorea
	Erythema marginatum	Erythema marginatum
	Subcutaneous nodules	Subcutaneous nodules
C.	**Minor criteria**	
	Low-risk populations∗	*Moderate- and high-risk populations*
	Polyarthralgia	Monoarthralgia
	Fever (≥38.5 °C)	Fever (≥38 °C)
	ESR ≥ 60 mm first hour and/or CRP ≥ 3.0 mg/dL[c]	ESR ≥ 30 mm/h and/or CRP ≥ 3.0 mg/dL[c]
	Prolong PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolong PR interval, after accounting for age variability (unless carditis is a major criterion)

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ARF acute rheumatic fever, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *GAS* group A streptococcus

[a]Subclinical carditis: echocardiographic valvulitis

[b]Major manifestation in moderate- to high-risk populations

[c]CRP value must be greater than the upper limit of normal for laboratory

[*]Low risk population for ARF as population known to experience low rates of ARF or RHD, or having an ARF incidence <2 per 100,000 school-aged children (5−14 years old) per year or an all-age prevalence of RHD of <−1,000 population per year.

populations and recognizing variability in clinical presentation in these high-risk populations. In addition, these revised criteria provide guidance on diagnosing recurrent ARF [51–53].

Laboratory evidence of a precedent group A streptococcal infection is needed whenever possible since other illnesses closely resemble ARF. Positive streptococcal serology might be difficult to interpret in populations with endemic skin or upper respiratory group A streptococcal infection. In this situation, a negative serology excludes a recent infection, but a positive test does not necessarily mean an infection in the recent past. In situations in which the levels of antistreptolysin O (ASO) titer are normal and in the presence of a high index of GAS infection suspicion, it is useful to perform other serologic tests to make precise an infectious precedent [54, 55]. Exceptions to Jones criteria include patients with chorea, insidious onset of carditis, and/or previous history of RF (rheumatic fever, heart disease) [56, 57].

Any one of the following can be used as evidence of a precedent streptococcal infection:

(a) Increased or rising ASO titer or other streptococcal antibodies (anti-DNase B). A rise in titer is a better evidence than a single titer result.
(b) A positive throat culture for group A beta-hemolytic streptococci.
(c) A positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis [58].

Laboratory testing might be of great assistance for the diagnosis of ARF, especially for the exclusion of other disorders. Anemia may be present in 10% of patients, leukocytosis and thrombocytosis too. Acute-phase reactants such as ESR and CRP allow the monitoring of disease activity and are usually normal in isolated cases of Sydenham chorea. An increase of two or more folds of basal levels of ASO is considered of significance regarding a previous streptococcal infection. Anti-DNase B antibodies are more adequate to use for diagnosis of Sydenham chorea since they are the last antibodies that return to normal levels following a streptococcal infection.

Clinical Manifestations

Minor Manifestations

The clinical picture of ARF is essentially similar in developing and developed countries [59, 60]. Carditis and arthritis remain the most common clinical manifestations during the first episode of ARF, followed by chorea, subcutaneous nodules, and, the least frequent, although highly specific, erythema marginatum [61–63]. There are, however, some reports from high-risk populations, such as the indigenous Australian population, in which unusual clinical manifestations appear to be frequent including aseptic monoarthritis, polyarthralgia, and low-grade fever (as opposed to high fever) [64–66].

Most patients with ARF, regardless of country of origin, will present with fever exceeding 38.5 °C orally. Two situations should be kept in mind, however: First, temperatures below 38 °C might be seen in certain aboriginal populations. Second, the widespread availability of antipyretic agents should be taken into consideration when evaluating patients with ARF [67].

Elevation of acute-phase reactants is a characteristic feature of ARF. Most patients exhibit ESR elevations above 60 mm/h and CRP > 3.0 mg/dL. It is very unusual to find normal ESR and CRP in patients suspected to have ARF, except in patients with chorea; and in the presence of normal ESR and CRP levels, other diagnostic considerations should be investigated.

Other minor clinical manifestations that may be present in ARF include tachycardia out of proportion to fever, rapid sleeping pulse rate, malaise, abdominal pain, anemia, epistaxis, leukocytosis, and anterior chest pain. Family history of rheumatic fever might also increase the index of suspicion.

Carditis

Carditis is the most frequent major clinical manifestation of ARF occurring between 40% and 80% and can affect any layer of the myocardium; valvular involvement is by far the most consistent clinical feature of ARF [68–70]. It is the most serious manifestation of the disease and might lead to death during the acute or chronic phase of ARF. The predominant finding in ARF is endocarditis; and recent clinical, echocardiographic, and histopathological observations have shown that heart failure is mainly due to valvular insufficiency and not myocarditis [71]. ARF occurs equally in males and females, although rheumatic heart disease is more frequently seen in females.

Clinical diagnosis of carditis is based on (a) auscultation of typical murmurs of recent onset indicative of mitral and/or aortic valve regurgitation (rare to find only aortic involvement) and the presence of (b) cardiomegaly secondary to myocarditis or secondary to hemodynamic changes due to valvular involvement and (c) congestive heart failure secondary to the presence of inflammatory or hemodynamic involvement. Clinical manifestations of carditis are variable and range from an insidious onset without significant manifestations to rapidly progressive heart failure. Heart involvement is unusual in adults, and when present clinical manifestations are benign [72, 73].

Electrocardiographic (ECG) abnormalities are relatively common and include conduction disturbance such as first-degree and less frequently second- and third-degree atrioventricular block and branch blocks. More than 50% of patients with ARF older than 17 years of age exhibit ECG abnormalities [74].

Echocardiography is a very useful tool in the study of patients with ARF; confirm mild to more severe valvular abnormalities by analyzing the blood flow with color Doppler and providing an estimation of the severity of the valvular involvement, myocardial function, and detection of pericardial thickening and fluid [75, 76]. In addition, monitoring of the cardiac abnormalities can be performed by transesophageal echocardiography. In recent years, the concept of subclinical carditis has been incorporated into guidelines and consensus reports as a valid rheumatic fever clinical manifestation to refer to those clinical circumstances in which physical findings of valvular dysfunction are not present or not recognized by clinicians but echocardiography/Doppler studies reveal mitral or aortic involvement [77, 78]. And according to the echocardiography/Doppler consensus report, this technique should be (a) performed in all cases of confirmed or suspected ARF, (b) serially performed in any patient with diagnosed or suspected ARF even if documented carditis is not present on diagnosis, and (c) performed to assess whether carditis is present in the absence of auscultatory findings, particularly in moderate- to high-risk populations and when ARF is considered likely; and (d) echocardiographic/Doppler findings not consistent with carditis should exclude that diagnosis in patients with a heart murmur otherwise thought to indicate rheumatic carditis [79].

Chest radiography might reveal cardiomegaly in the presence of cardiac insufficiency or pericardial effusion.

Arthritis

Arthritis is the most common and early clinical manifestation, present in about 80% of patients, and generally involves the large joints, shoulders, knees, ankles, elbows, and wrists. The classical description is migratory polyarthritis, extremely painful despite lack of significant clinical articular findings, short duration of 2–4 weeks, and excellent response to salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs). Synovial fluid exhibits inflammatory characteristics with leukocyte counts between 20,000 and 40,000 cells/μL with predominant polymorphonuclear cells. Complement C3 and C4 components are diminished in synovial fluid suggesting immune complex activation. Long-term prognosis is good, and majority of patients do not develop joint deformity; however, some patients develop a chronic, deforming polyarthritis of the small joints of the hands and feet with reversible ulnar deviation, so-called Jaccoud arthritis [80, 81].

Aseptic Monoarthritis

Aseptic monoarthritis or oligoarthritis affecting the large joints of the lower extremities, hip, knee, and/or ankle is increasingly recognized in high-risk populations, India, Fiji, Australia, and other Asian countries [82, 83]. In some series, up to 55% of patients eventually diagnosed with ARF presented with monoarthritis or oligoarthritis [84]. In addition, there is a small series with three pediatric patients reported from Utah [85]. At present, consideration that monoarthritis or oligoarthritis may be part of the ARF clinical spectrum should be limited to patients from moderate- to high-risk populations.

Post-streptococcal Reactive Arthritis

Patients with group A beta-hemolytic streptococcal infection and articular involvement not fulfilling the classic Jones criteria for the diagnosis of ARF are classified as having post-streptococcal reactive arthritis [86–88]. The clinical picture in post-streptococcal reactive arthritis exhibits variable expression, and to many it is considered as part of the spectrum of ARF, but some publications suggest otherwise.

The most important clinical characteristics are (a) shorter period of latency between onset of infection and appearance of clinical manifestations, 1–2 weeks; (b) higher proportion of involvement of small and axial joints; (c) poor clinical response to salicylates and AINEs; (d) prolonged non-migratory arthritis; (e) low incidence of carditis with late onset in 6% of cases; and (f) absence of major Jones criteria. Some patients with post-streptococcal reactive arthritis have later developed both ARF and RHD, but a series from the Netherlands was not associated with long-term cardiac sequelae [89]. In addition, it has been shown that ARF is associated with the DRB1∗16 allele, while DRB1∗01 is more common in patients with post-streptococcal reactive arthritis [90].

Polyarthralgia

Polyarthralgia used to be considered a major criterion for the diagnosis of ARF. But it was eventually reclassified as a minor criterion to maintain Dr. Jones's original intention not to overdiagnose ARF. Actual consensus found no compelling evidence to amend this conclusion in low-risk populations. But clinicians in high-risk populations should keep in mind that ARF might be present in children presenting with polyarthralgia [91].

Chorea (Sydenham Chorea)

Chorea is an extrapyramidal manifestation that occurs in 30% of patients with ARF and characterized by rapid involuntary movements, erratic and without a purpose, which subside during sleep [92, 93]. It usually involves muscles of the face and extremities. It is frequent to be associated with neuropsychiatric abnormalities, compulsive-obsessive behavior, muscle weakness, and mood alterations. Chorea symptomatology remits spontaneously in half of patients at 2–3 months of evolution, but benign symptomatology may persist for more than 2 years. Documentation of a recent group A streptococcal infection may be difficult to confirm due to the long latency period between the triggering infection episode and onset of chorea.

A latency period of up to 6 months between group A streptococcal infection and chorea suggests an autoimmune etiology-mediated tissue injury. The presence of antibodies against basal ganglia (subthalamic and caudate nuclei) in a significant proportion of patients with acute chorea allows monitoring by ELISA to assess response to therapy and prognosis [94–96].

Differential diagnoses are wide; and a careful neurologic examination is needed to exclude other neurological disorders including Huntington chorea, systemic lupus erythematosus, anti-phospholipid syndrome, thyrotoxicosis, Wilson disease, cerebrovascular accidents, drug reactions, tics, athetosis, hyperkinesia, and conversion reactions.

Cutaneous Manifestations

Erythema marginatum is a specific clinical manifestation present in about 7% of patients with ARF, and when present it strongly suggests the coexistence of carditis [97]. Lesions are characteristically evanescent, pink, and maculopapular with pale centers and circular or serpiginous borders, not associated with itching or pain, are blanched on digital pressure, and go away in a matter of days. Lesions are localized to the trunk, abdomen, and medial aspect of arms and thighs and do not involve the face. Rash can be difficult to detect in dark-skinned individuals.

Subcutaneous nodules are painless protuberances that can be seen isolated or in crops, along extensor surfaces of the elbows and knees, bony prominences such as the occiput, and spinous processes of the thoracic and lumbar spine and tendons. They occur in about 8% of patients with ARF, often associated with carditis and seldom seen as the only manifestation of ARF [98].

Differential Diagnosis

Differential diagnosis of ARF is wide, and multiple systemic inflammatory conditions need to be considered, depending on the major manifestations present. The use of echocardiography/Doppler studies in the diagnosis of subclinical carditis requires a good understanding of clinical and echocardiographic findings that could resemble rheumatic carditis, especially in low-risk populations.

Differential Diagnosis of Acute Rheumatic Fever

A. **Systemic Musculoskeletal Disorders**
   - Septic arthritis
   - Sickle cell anemia
   - Juvenile idiopathic arthritis
   - Post-streptococcal reactive arthritis
   - Lyme disease
   - Viral arthritides
   - Lymphopoietic malignancy: leukemia

B. **Cardiovascular Disorders**
   - Kawasaki disease
   - Viral myocarditis
   - Idiopathic myocarditis
   - Infective endocarditis
   - Cardiomyopathy
   - Mitral regurgitation
   - Congenital valvular disease

C. **Neurological Disorders**
   - Encephalitis
   - Wilson disease
   - Lyme disease
   - Anti-phospholipid syndrome
   - Huntington disease
   - Choreoathetoid cerebral palsy
   - Brain malignancy
   - Drug intoxication

Treatment

The primary goal in the treatment of ARF is eradication of the inciting GAS infection of the upper respiratory tract [99–101]. Simple clinical improvement of the pharyngeal infectious process is not enough to achieve effective prevention; and it is necessary to eliminate GAS infection by an adequate use of antibiotics. Penicillin is the antibiotic of choice, and a single dose of 600,000 units of benzathine penicillin administered intramuscularly in children weighing less than 27 kg of body weight and 1.200,000 units to those above suffices to achieve eradication. Oral administration of penicillin V or phenoxymethylpenicillin for 10 days can also be administered. Main contraindications to the use of benzathine penicillin are allergy and coagulation abnormalities such as thrombocytopenia. Erythromycin can be used in the presence of allergy to penicillin at a dose of 40 mg/kg/day divided in two to four daily doses for a total of 10 days. Newer macrolides such as azithromycin have an advantage of being better tolerated by the GI tract and can be used for only 5 days, but their use has been associated with resistance and treatment failure. Derivatives of sulfa drugs should not be used due to their inability to eradicate GAS infection.

The next step in the treatment of ARF is to prevent recurrence. This entails primary and secondary preventive measures aimed to eradicate GAS infection. Improved economic conditions leading to better living conditions including housing and reduced household overcrowding probably are responsible for the decline in mortality due to ARF and RHD observed in develop countries [102–104].

Prevention and treatment of GAS infection including recurrent GAS infection are other measures to reduce ARF and RHD. It is necessary to use continually anti-streptococcal prophylaxis because many infections able to reactivate rheumatic fever are asymptomatic and individuals who have suffered ARF remain at risk of recurrence in ensuing years. Benzathine penicillin at the recommended doses for eradication given every 3–4 weeks has been shown to be an effective and safe modality for primary and secondary prophylaxis. To prevent new attacks, the American Heart Association recommends benzathine penicillin every 3 weeks to individuals at high risk and for those living in endemic areas.

Primary antibiotic prophylaxis using intramuscular penicillin to eradicate GAS infection before it can induce ARF has been shown to be effective and cost-effective, especially in regions where both the incidence of ARF and program effectiveness were high, but the practicality and cost-effectiveness of such programs in low-income countries is subject to debate [105].

Regarding secondary antibiotic prophylaxis, good evidence of efficacy and effectiveness is lacking [106]. There are no good-quality studies demonstrating efficacy of secondary antibiotic prophylaxis. However, there is data demonstrating that intramuscular benzathine penicillin reduces ARF recurrences as compared with oral penicillin. But no randomized clinical trial evidence supports secondary prophylaxis to prevent disease progression. It has been suggested that secondary prophylaxis may potentially be more useful in patients with mild valvular disease.

Considering available evidence, it has been recommended that antibiotic prophylaxis should be continued for 10 years or up to the age of 40 years. It is very unusual to have recurrence of ARF beyond this age.

Although the efficacy of oral antibiotics to eradicate GAS infection is a matter of controversy, it is possible to administer oral penicillin at 250 mg twice daily; erythromycin is useful at the same doses, in situations when there is allergy to penicillin.

Family members of patients with a history of or active ARF should also be appropriately treated. Other clinical manifestations of ARF such as fever, arthritis/arthralgia, carditis, and chorea should also be managed appropriately. Vaccine development is still a work in progress.

Constitutional complaints including fever and malaise respond well to salicylates, NSAIDs, or paracetamol.

Musculoskeletal manifestations and arthritis/arthralgia rapidly respond to salicylates and other NSAIDs, and if articular manifestations do not respond within 72 h, another condition should be considered. Treatment should be given for at least 4 weeks but can be extended to 12 weeks. Steroids may be occasionally used and provide rapid relief of both arthralgia and arthritis and decline of inflammatory markers including ESR.

Rheumatic carditis usually manifests with mild or moderate mitral regurgitation, and severe involvement may precipitate heart failure and should be treated with oral prednisone at a maximal dose of 60 mg daily for at least 2 weeks, and then it should be slowly and progressively tapered down over the ensuing weeks. Concomitant use of salicylate and/or NSAIDs should be given to avoid a rebound of disease activity to tapering of prednisone, and they should be continued at least for a month following discontinuation of prednisone. In vitro evidence has shown that hydroxychloroquine by suppressing IL-1B expansion of GM-CSF-expressing CD4 T-cells might be used to reduce the risk of rheumatic heart disease following ARF [38]. Appropriate treatment of heart failure should also be given. Complete rest is recommended for at least 4 weeks to facilitate full recovery.

Chorea may present without other features of ARF, and spontaneous resolution can occur in most patients within the first few months of illness. Good symptomatic improvement follows initiation of haloperidol at doses of 0.5–1.0 mg/day, with increments of 0.5 mg every 3 days if there is no satisfactory clinical response. Carbamazepine and sodium valproate are also effective and with less side effects.

For refractory cases, prednisone, plasmapheresis, and IV immunoglobulin can be used. Evidence about their efficacy comes from small series and/or case reports; and prospective, randomized, double-blind clinical trials are needed to confirm efficacy, cost-effectiveness, and safety profile [107–109].

Management of Acute Rheumatic Fever (ARF)

A. **Accurate and Prompt Diagnosis**
   Streptococcal serology
   Acute-phase reactants: ESR, CRP
   Echocardiographic assessment of heart involvement
   Diagnostic investigation to rule out other diagnoses
B. **Eradication of Group A Streptococcus Pharyngitis**
   Intramuscular dose of benzathine penicillin G
C. **Management of Constitutional and Musculoskeletal Manifestations**
   Acetaminophen
   Non-steroidal anti-inflammatory drugs
D. **Management of Cardiovascular Involvement**
   Appropriate bed rest, fluid restriction, and diuresis
   Glucocorticoids for severe cardiac involvement including heart failure
E. **Management of Chorea**
   Rest
   For severe or refractory situations: valproic acid, carbamazepine or glucocorticoids, plasmapheresis, or IV IgG infusions
F. **Long-Term Prevention**
   Benzathine penicillin G
   Proper education

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Pathophysiology of Reactive Arthritis

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Introduction

Reactive arthritis (ReA), is characterized by the onset of arthritis following an infection elsewhere in the body. It most commonly presents as an oligoarthritis following infections of the genitourinary or gastrointestinal tract. Besides arthritis, disease manifestations can include dactylitis, enthesitis, and sacroiliitis. In the past, it was differentiated from septic arthritis on the basis of the fact that the causative organism could not be cultured from the inflamed joint. Overtime, with identification of both bacteria and bacterial products from the joints, this view has changed although no definition has yet been agreed upon for this form of arthritis [1]. An international consensus workshop that attempted to define reactive arthritis described two major and two minor criteria for classification. The major criteria included mono- or oligoarthritis that was asymmetric and involved joints in the lower limbs and symptomatic infection in the form of enteritis or urethritis for at least a day, 3 days to 6 weeks before the onset of arthritis. The minor criteria included evidence of infection in the form of stool cultures positive for enteropathogenic bacteria associated with ReA or positive nucleic acid amplification or urethral/cervical swabs for *Chlamydia*. Alternatively, they included evidence of persistent synovial infection in the form of a positive polymerase chain reaction assay for *Chlamydia* or evidence of *Chlamydia* on immunohistologic analysis. To classify as definite ReA, patients needed to satisfy both major criteria and at least one minor criteria. Presence of both major but no minor criteria or one major with one or more minor criteria was classified as probable ReA [1].

Although not the first description of the triad of urethritis, conjunctivitis, and arthritis, the description of this triad by Hans Reiter in a German soldier [2] was given the eponym Reiter's syndrome by Bauer and Engleman [3]. In recent years however, the term has been replaced by ReA, in part because of Reiter's association with war crimes in the Second World War. During that war, Paronen et al. described the outbreak of *Shigella* dysentery and reported that less than 1% of affected individuals developed arthritis following the infection [4]. Associated with post-streptococcal pharyngitis, acute rheumatic fever is also thought to be a form of ReA. John Zabriskie first showed cross-reactivity between streptococcal wall antigens and cardiac proteins, suggesting molecular mimicry may play a role in disease pathogenesis in acute rheumatic fever [5].

The identification of HLA-B27 as a risk factor for both reactive arthritis and ankylosing spondylitis (AS) [6] further has been cited as supporting the concept of molecular mimicry in disease pathogenesis. Sequence homology between B27 and arthritogenic microbes or monoclonal antibodies and T-cell clones reacting to both B27 and causative organisms [7, 8] has been invoked as a link between infection and subsequent arthritis.

Identification of Etiological Agents in Reactive Arthritis

Some of the well-defined bacteria associated with ReA following diarrheal illness include various serovars of *Salmonella*, *Shigella (flexneri*, *sonnei*, and *dysenteriae)*, *Campylobacter jejuni* and *C. coli*, *Yersinia enterocolitica* and *Y. pseudotuberculosis*, *Clostridium difficile*, and *Escherichia coli*. Organisms causing urogenital infections include *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_32

Mycoplasma genitalium. Those associated with respiratory infections include group A β-hemolytic streptococci and *Mycoplasma pneumoniae* [1].

While a diagnosis of septic arthritis, following Koch's postulates, relies on isolation of the causative organism from the affected joint, a diagnosis of ReA relies on a history of infection at a distant site a few days to weeks before the onset of synovitis or the pathogen being isolated from this site at the time of infection. Typically, the pathogen cannot be cultured from the joint in ReA; but with advances in technology, organisms such as *Chlamydia* have been demonstrable on electron microscopy in addition to chlamydial DNA being isolated through in situ hybridization and chlamydial RNA through reverse transcriptase PCR. Immunofluorescence studies revealed components of *Yersinia* and *Salmonella* in synovial fluid of ReA patients suggesting that persistence of microbial fragments may play a role in disease pathogenesis [9]. Furthermore, muramic acid, the peptidoglycan component of the bacterial cell walls, has been identified by gas chromatography and mass spectrometry analysis in synovial fluid from patients with post-*Salmonella* ReA. The ability of cell wall components to induce experimental ReA in rat models suggested a structural basis for arthritogenicity [10]. Bacterial peptidoglycans can induce synovial macrophages to express co-stimulatory molecules CD80 and CD86 as well as inducing pro-inflammatory cytokines [11]. Cell wall components such as peptidoglycans and lipopolysaccharides act as ligands to toll-like receptors (TLRs) [10]. These components have also been found in other inflammatory conditions such as rheumatoid arthritis and noninflammatory conditions such as osteoarthritis [12]. However, the susceptibility to gram-positive and gram-negative infections in those with polymorphisms for TLR2 [13] and TLR4 [14], respectively, would suggest a causative role in disease pathogenesis of reactive arthritis.

Innate Immunity and Development of ReA

The discovery of TLRs as the gate keepers of the innate immune system providing the first line of defense against pathogens led to focusing attention on why some individuals exposed to pathogens develop ReA, while others do not. TLR2 is a receptor for cell wall components for a number of bacteria. Initial reports recognized polymorphisms in TLR2 as a cause of susceptibility to staphylococcal infections and sepsis [13]. A more recent report found that single-nucleotide polymorphisms in TLR2 but not TLR4 predisposed to development of arthritis in a group of 75 patients with *Salmonella enteritidis* infection [15]. Thus, the presence of cell wall components alone in the absence of the intact pathogen may be enough to trigger an inflammatory response leading to chronic arthritis.

Animal models such as the B27 transgenic rats that mimic spondyloarthritis with involvement of the gut, skin, and joints provide some support for this hypothesis [16]. These features have been shown to be attenuated if these rats are raised in a germ-free environment [17]. Challenging these animals with a gut commensal such as *Bacteroides* is enough to reestablish clinical features of arthritis in this model of arthritis. Another example is the mice deficient in interleukin-1 receptor antagonist (IL-1Ra) which normally develop an aggressive form of arthritis, but when raised in a germ-free environment, the arthritis does not develop [18]. Reestablishing arthritis in this animal model only requires a TLR ligand. Studies have shown varied effects of TLR signaling in the gut in this model with TLR4 signaling leading to exacerbation of arthritis and TLR2 having a modulatory effect. The importance of the gut as a site for trigger of events is also highlighted by the fact that the same genetic variants confer disease susceptibility to both AS and Crohn's disease [19]. Subclinical gut inflammation with upregulation of IL-23 expression is common in patients with AS [20].

Host Response and the Role of Cytokines in Reactive Arthritis

It was previously thought that the host immune response to infection in ReA was overactive, but studies have shown that the opposite may be the case, at least in acute ReA. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-ɣ) have been shown to be reduced instead of being elevated in acute ReA [21]. In animal models of ReA, animals with increased susceptibility to *Chlamydia*-induced arthritis show lower levels of these pro-inflammatory cytokines in their joints suggesting an impaired capacity to clear these organisms by the host, contributing to susceptibility to joint inflammation [22]. While this is genetically determined, environmental factors such as exposure to heavy metals have been shown to alter the host immune response [23]. A similar defective host response is also seen in Crohn's disease where genetic susceptibility is related to polymorphisms in the *CARD15* gene resulting in diminished macrophage function and *reduced* production of pro-inflammatory cytokines such as TNF-α [24]. Conversely, others have shown that in chronic stages of ReA, TNF-α levels may be elevated [25] which suggests a dual role of this cytokine in different stages of disease pathogenesis. This may also explain the efficacy of anti-TNF therapy in ReA.

Another important cytokine in the pathogenesis of ReA is IL-17, which is produced by Th17 cells. Higher concentrations of IL-17-positive CD4+ T-cells [26] as well as IL-17 levels [27] were found in the synovial fluid of patients with *Chlamydia*-induced ReA. *Salmonella*-induced ReA in mice has also been shown to be dependent on CD4+ T-cells

secreting IL-17 [28]. This cytokine also plays a major role in *Yersinia*-induced ReA, with neutralization of IL-17 leading to abrogation of arthritis [29]. Others have shown that consumption of *Lactobacillus casei* prior to *Salmonella* infection in mice modulates the IL-23/IL-17 expression and abolishes both gut and joint inflammation [30]. IL-12 deficiency has also been shown to have a relationship with ReA. The balance between IL-12 and IL-10 may play a role in reduced bacterial clearance from joints leading to susceptibility to ReA [31]. Mice deficient in the p40 subunit of IL-12/IL-23 develop ReA after oral intake of *Yersinia enterocolitica* suggesting a protective role for IL-12 and IL-23 in ReA [32].

IL-10 is an anti-inflammatory cytokine produced predominantly by regulatory T-cells but also by CD4+ T-helper cell subsets. Compared to RA, the levels of IL-10 and TGF-β were higher and those of TNF-α lower, in cases of ReA with disease duration of 6 months [33]. An association between IL-10 promoter polymorphisms and ReA has also been found, suggesting this may lead to persistence of pathogenic bacteria [34].

HLA-B27 and Molecular Mimicry

HLA-B27 is an allele of the polymorphic class I MHC molecules that present peptides derived from intracellular proteins to the T-cell receptor on CD8+ cytotoxic T-lymphocytes (CTLs). The association between HLA-B27 and ReA is well known, but its role in pathogenesis remains unclear. A number of theories have been proposed, including molecular mimicry due to similarity between amino acid sequences in HLA-B27 and *Yersinia* or *Shigella* proteins leading to cross-reactivity, tolerance, and hence persistence of the organism [35].

B27-restricted bacteria-specific CD8+ cells from inflamed joints of patients with ReA were isolated using a panel of αβ-T-cell receptor CD8+ T-lymphocyte clones that killed *Yersinia*- and *Salmonella*-infected B27 target cells. This study also showed development of autoreactive CTLs which showed B27-restricted killing of uninfected cell lines [7].

A subsequent study identified an immunodominant epitope derived from *S. typhimurium* GroEL molecule [36]. This epitope was presented by the mouse nonclassical MHC class Ib molecule Qa1 and recognized by CD8+ CTLs after natural infection. *S. typhimurium*-stimulated CTLs recognizing the GroEL epitope cross-reacted with a peptide derived from mouse heat shock protein 60 and recognized activated macrophages. This indicated MHC class Ib molecules in infection induced an autoimmune recognition event, providing a link between gram-negative bacterial infection and autoimmunity. Although this study showed shared sequence homology between host and pathogen, it failed to show specificity of functional cross-reactivity in the absence of controls for CTLs from mice infected with other organisms or uninfected mice [37].

Role of the Gut Microbiome in ReA

In recent years, there has been a growing interest in the gut microbiome and its role in the pathogenesis of arthritis. Deviation of microbial composition, also called microbial dysbiosis, occurs in inflammatory and autoimmune diseases, although it is unclear whether this is the result of inflammatory change or whether it mediates epithelial involvement [38]. Inflammatory bowel disease, psoriasis, and SpA are all characterized by gut dysbiosis. While all of these conditions show decreased gut bacterial diversity, this is not the case in ReA. In a study that compared patients with ReA with those with prior infections who did not go on to develop arthritis [39], no significant differences were seen in gut bacterial diversity between the groups. *Erwinia* and *Pseudomonas* as well as other enteropathogens, such as *Salmonella*, *Shigella*, and *Campylobacter*, were significantly higher in abundance in ReA than in controls. Differences were observed on the basis of clinical features with those presenting with enthesitis on ultrasound being enriched with *Campylobacter* while those with uveitis and radiographic sacroiliitis being enriched with *Dialister* [39]. The latter has been shown to be associated with disease activity in AS [40].

Host genetics also play an important role with presence of the allele HLA-A24 being associated with abundance of *Prevotellaceae* while those being HLA-A24 negative showing an abundance of *Rikenellaceae* and *Ruminococcaceae* [39]. *Prevotella* is associated with RA [41]; and it may be that the presence of *Prevotella* and the HLA-A24 allele, along with the concomitant reduction in beneficial gut-protective commensals, may also contribute to the development of ReA. Commensal microorganisms exert anti-inflammatory effects on the gut by fermenting dietary fibers to produce short-chain fatty acids which decrease expression of pro-inflammatory cytokines [42] and promote regulatory T-cell responses [43, 44].

Metabolomic Patterns in Reactive Arthritis

Metabolomic studies have shown patterns of metabolites that are common to different forms of inflammatory arthritis. Elevated levels of glucose and lactate are seen to reflect dampened glycolysis to maintain the inflammatory state by inducing oxidative stress [45, 46]. Hyperglycemia elevates inflammatory cytokines such as TNF-α, IL-1, IL-6, and IFN-ϒ as well as activation of NF-κB [47]. In systemic inflammatory conditions, muscle tissue and the liver release high quantity of amino acids in the circulation for maintenance of cellular homeostasis. Amino acids such as glutamate, isoleucine, leucine, histidine, and citrulline are elevated in RA, while others such as glutamine, phenylalanine, and valine

are decreased in this condition [45]. Glutamine is consumed as a substrate by macrophages and converted to glutamate suggesting glutaminolysis is active in RA.

In a recent study, increased serum levels of leucine, isoleucine, citrulline, glutamate, 3-hydroxybutyrate (HB), glycine, glucose, creatine, and histidine were found in ReA patients [45]. Serum levels of lipid and membrane metabolites such as LDL, VLDL, choline, and PUFA were decreased. This is similar to findings from previous studies in RA suggesting similar immune-inflammatory dysregulation [48]. However, unlike RA controls in the study, serum levels of phenylalanine and valine were elevated in ReA. Levels of branched-chain amino acids (BCCA) are elevated in conditions such as sepsis; and increased levels promote oxidative stress, inflammation, and migration of peripheral blood mononuclear cells via mammalian target of Rapamycin Complex 1 (mTORC1) activation. The reduced serum levels in RA may suggest it may serve as an alternative substrate for the TCA cycle under suppressed activity of glyceraldehyde 3-phosphate dehydrogenase, resulting in dampened glycolytic activity [49]. The increased serum levels in ReA may suggest dominance of protein degradation in this condition [45]. Phenylalanine is converted to tyrosine under aerobic conditions. A correlation between reduced phenylalanine turnover, resulting in increased serum levels, and inflammation has been reported [50]. Reduced activity of phenyl-4-hydroxylase results from oxidative stress secondary to immune activation and inflammation [51].

Reduced levels in serum of membrane and lipid metabolites observed in both RA and ReA may be as the result of their increased utilization in the synthesis of inflammatory mediators that drive the immunometabolic response, β-oxidation of fatty acids to meet energy demands in systemic inflammation, and their utilization in the repair of membranes of cells and organelles affected by inflammation and oxidative stress [45].

Chlamydia-Induced Reactive Arthritis

Chlamydia-induced reactive arthritis (CiReA) is the most common form of reactive arthritis with 4–15% of those with genital chlamydial infections going on to develop arthritis. Although previously thought to result as an autoimmune reaction to an extra-articular infection, the discovery of *Chlamydia* in an aberrant but viable state using nucleic acid detection and electron microscopy has led to a paradigm shift in disease pathogenesis. The initial paradigm of tissue damage as a result of an aberrant response to activation of the adaptive immune system through delayed hypersensitivity or autoimmunity [52] has shifted toward an inflammatory response propagated by sustained infection of nonimmune cells with inflammatory mediators and subsequently recruited inflammatory cells causing tissue damage [53]. This also brings up a contradiction in the classification of *Chlamydia*-induced ReA. Supporting the concept of CiReA being a septic arthritis is the fact that combination antibiotics have been shown to change the course of ReA [54]. The immunopathogenesis of CiReA recapitulates that of septic arthritis with mediators of susceptibility and the role of the immune system [55, 56].

Monocytic cells are known to carry *Chlamydia* [57] from the primary site of infection to various tissues including the liver, spleen, peritoneum, and lungs [58]. However, unlike the joint, *Chlamydia* is cleared from these sites. Like the genital tract, the inflamed joint provides an immune privileged relatively hypoxic microenvironment in which *Chlamydia* are known to thrive [59]. *Chlamydia* are adapted to grow under these conditions, due to their ability to manipulate hypoxia-inducible factor 1 (HIF-1) [60]. Antibiotics as well as bactericidal cytokines such as IFN-ɣ also are less effective in clearing the organism under hypoxic conditions leading to its persistence [61].

Chlamydia exists in two different forms, as an obligate intracellular replicative reticulate body and an extracellular, infectious elementary body [62]. When exposed to stress such as IFN-ɣ and antibiotics, the intracellular state enters a non-replicative, unculturable but viable persistent state. In this persistent state, *Chlamydia* show reduced metabolism, fail to differentiate into the infectious particle, and evade the immune system [63]. Although the persistent state cannot be cultured from synovial biopsies [64], it shows a unique gene expression profile and can be identified using quantitative PCR [65].

It remains unclear if the persistent state is the cause of ReA or the effect of a host-pathogen adaptation. Persistent *Chlamydia* may act as a continuous source of bacterial components stimulating the immune system causing chronic inflammation [66]. Alternatively, persistence may represent the host's attempt at containing *Chlamydia*, with disease flares being related to chlamydial escape from persistence leading to acute inflammatory events [67].

Factors That Mediate Susceptibility to Chlamydial Infections

Susceptibility to chlamydial infections depends on pathogen, host, and environmental factors. The outer membrane protein of the pathogen that dictate chlamydial biovar is associated more with tissue tropism rather than virulence, although unexpectedly ocular biovar has been more commonly detected than genital biovar in ReA [68]. The significance of non-biovar variance remains undetermined [69]. Consistent rates of *Chlamydia*-related disease suggest that alteration in chlamydial pathogenicity is uncommon.

Environmental factors such as structural abnormality of the genital tract are associated with recurrent chlamydial infection [70]. Clinically, as one cannot distinguish between recurrent and chronic chlamydial infections, it is difficult to ascertain whether repeated infections are required to develop CiReA [71]. Heavy metal exposure in animals otherwise resistant to CiReA leads to suppression of pro-inflammatory cytokines such as TNF-α and IFN-ɤ and increased susceptibility to CiReA [23].

Host factors also play an important role, as up to 80% of chlamydial infections are asymptomatic [72]. Genetic variability that predicts a robust type 1 (classical) inflammatory response is protective against *Chlamydia*, while that predicting an enhanced type 2 (alternate) inflammatory response increases susceptibility to chlamydial infection (Fig. 32.1) [73]. This has been demonstrated both in animal models [22] and human studies where sequelae are reported with higher type 2 immune cytokine response [74] and patients experiencing prolonged ReA showing lower levels of type 1 cytokines such as IFN-ɤ, than those that rapidly overcome ReA [21].

Innate Immunity in *Chlamydia*-Induced Reactive Arthritis

An effective immune response to *Chlamydia*, and resistance to CiReA, is associated with a robust type 1 cytokine response as early as 3 days after infection [75, 76]. Hence, the adaptive immune system is unlikely to play a role in disease susceptibility. Natural killer T-cells (NKT cells), neutrophils, as well as macrophages mediate the innate immune response. NKT cells produce IFN-ɤ providing early protective effect [77], while neutrophils reduce early excessive chlamydial growth [78]. Excessive activation of neutrophils can lead to tissue damage and CiReA [79]. Depletion of another cell involved in innate immunity, the macrophage, leads to progression of infection [80] and in animal models was associated with increased risk of dissemination of infection from its original site [81]. Macrophages, based on phenotype and function, can be classified as either being classically activated (M1) or alternatively activated (M2). Foxp3+ regulatory macrophages have also been described. M1 macrophages control [82] and M2 macrophages permit chlamydial growth [83].

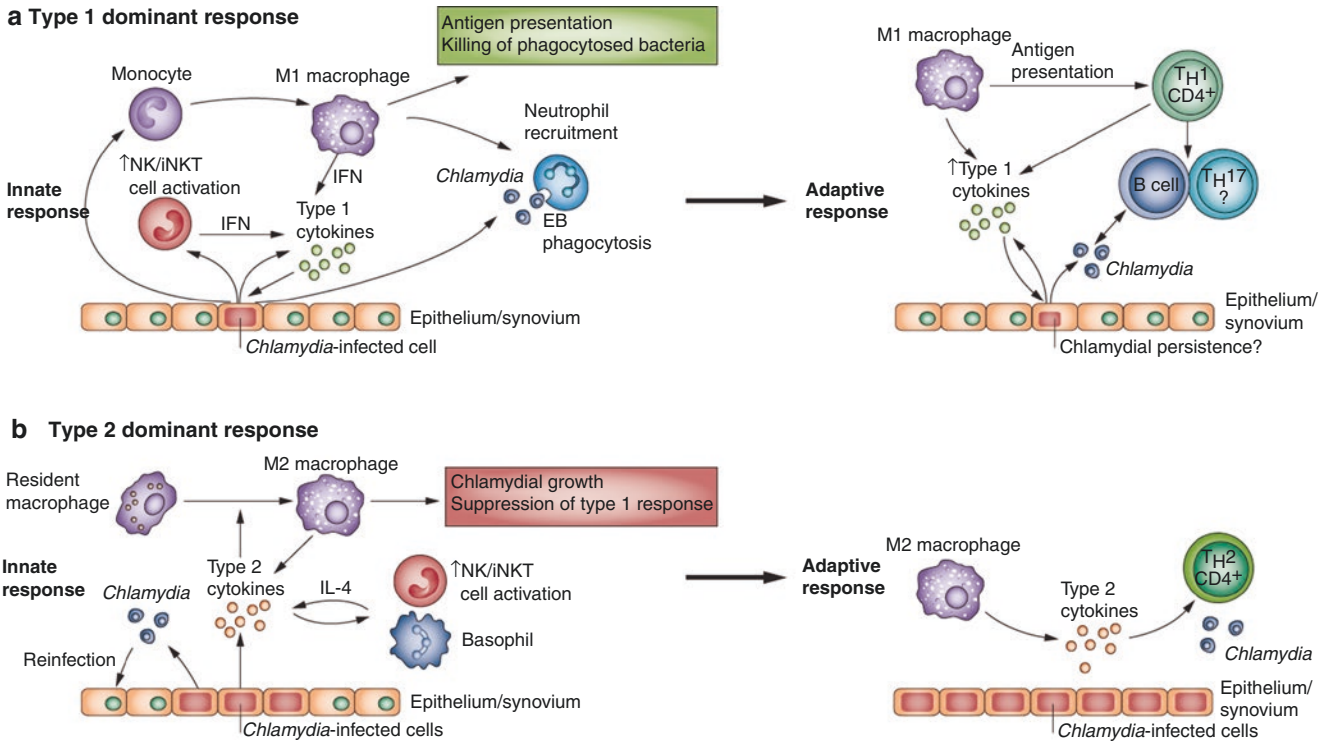

Fig. 32.1 The role of macrophages in *Chlamydia*-induced arthritis. (**a**) A type 1 response with activation of M1 macrophages leading to effective control of *Chlamydia* and induction of persistence. (**b**) Type 2 dominant response with excessive chlamydial growth due to an ineffective innate and adaptive immune response. Abbreviations: EB, elementary body; IFN, interferon; NK cell, natural killer cell; INKT cell, invariant natural killer T-cell; TH1, type 1 helper T-cell; TH2, type 2 helper T-cell; TH17, type 17 helper T-cell. (From Gracey and Inman [73], *Nature Reviews Rheumatology*)

Conclusions

Studying ReA remains challenging with many questions regarding disease pathogenesis remaining unanswered. It is still not clear why only a small percentage of individuals exposed to the pathogens go on to develop ReA. While it is clear that an imbalance between Th1 and Th2 responses plays an important role in disease pathogenesis with components of the innate immune system being key players, factors leading to disease chronicity and recurrence need further clarification. The role of gut microbial dysbiosis in disease pathogenesis remains unclear. Further investigation of host genetics and serum and synovial fluid metabolomics from patients may hold important clues to further understanding disease pathophysiology.

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The Major Histocompatibility Complex and Reactive Arthritis

33

Benjamin S. Naovarat and John D. Reveille

Overview

The major histocompatibility complex (MHC) is one of the most intensely studied regions in the human genome. Spanning four megabases on the short arm of chromosome 6 (6p21.3), it contains the most polymorphic genes in the human genome (Table 33.1), which are involved in many critical aspects of the innate immune response, including transplantation and defense against infection, and in most immune-mediated and autoimmune diseases. In this era where genome-wide association studies have extensively dissected the genetic basics of many of the rheumatic diseases, in most instances, most of the genetic variance is attributable to the MHC.

In the 45 years that have passed since the first description of the association of HLA-B27 with reactive arthritis [1], intense investigation has ensued studying the roles of this remarkable molecule and other MHC genes and susceptibility to spondyloarthritis (SpA) (summarized in references [2–6]). First of all, although at least a third of the genetic variance in SpA susceptibility has been attributed to HLA-B27 and other genes of the MHC and HLA-B27 has been shown to play a variety of roles in pathogenesis, how HLA-B27 actually causes ReA is still unknown, although current evidence suggests it may influence disease susceptibility by different mechanisms.

This chapter will present an overview of the MHC and its organization and explore how HLA-B27 and other genes of the MHC may influence susceptibility and outcome in reactive arthritis.

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Organization of the Major Histocompatibility Complex (MHC)

The 4-Mb human MHC (also known as the HLA complex) encodes over 220 genes, many of which are involved in the immune response, graft rejection, and disease susceptibility. Most prominent of these include HLA class I and II molecules, which initiate the cell-mediated immune response by displaying antigenic oligopeptides to the αβ-T-cell receptor. This interaction is critical in combating microbiological invasions, controlling malignant cell proliferation, and governing transplant success [7] (Fig. 33.1).

MHC Class I Region (Fig. 33.2)

The MHC contains not only the "classical" HLA class I genes (HLA-A, HLA-B, and HLA-C), whose products present peptides to CD8-positive T-cells and natural killer (NK) cells, but also a several "nonclassical" class I genes (MICA, MICB, HLA-E, HLA-F, and HLA-G), pseudogenes (HLA-H, HLA-K, HLA-J, HLA-N), and class I gene fragments (HLA-L, HLA-P, HLA-S, HLA-T, and HLA-W). These additional class I genes vary between species, and their functions are unknown, although it is likely that they have a role in contributing to the sequence diversity of other class I genes. Also contained in the MHC class I region are genes involved in other immunologic functions (immune early response (IER) and ATP-binding cassette subfamily F member 1 (ABCF1) genes).

"Classical" MHC Class Ia Genes

The HLA class I genes are involved in antigen presentation. HLA-A, HLA-B, and HLA-C in humans are highly diverse, whereas other class I genes are of much more limited diversity. They are the most polymorphic in the human genome (Table 33.1), reflecting their primary role in interfacing with an ever-changing environment, and serve especially in antiviral and other infectious immunity and immune tolerances

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_33

Table 33.1 Polymorphism of MHC genes, March 2019

Gene	Alleles	Proteins	Null genes
A	4846	3286	255
B	5881	4088	190
C	4654	3070	185
E	27	8	1
F	38	6	0
G	61	19	3
H	12	0	0
J	9	0	0
K	6	0	0
L	5	0	0
N	5	0	0
P	5	0	0
S	7	0	0
T	8	0	0
U	5	0	0
V	3	0	0
W	11	0	0
Y	3	0	0
DRA	7	2	0
DRB	2841	2043	99
DQA1	114	46	4
DQB1	1498	1007	46
DPA1	85	32	0
DPA2	5	2	0
DPB1	1312	868	64
DPB2	6	3	0
DMA	7	4	0
DMB	13	7	0
DOA	12	3	1
DOB	13	5	0

Data from Robinson et al. [139, 140]. Available at https://www.ebi.ac.uk/ipd/imgt/hla/stats.html

(such as is encountered in transplantation and cancer). This diversity is reflected not only in the polymorphism of proteins expressed at the cell surface (the result of nonsynonymous substitutions, which is a nucleotide mutation that alters the amino acid sequence of a protein) but also synonymous substitutions which do not alter amino acid sequences but result in an increased number of alleles compared to proteins.

"Nonclassical" MHC Class Ib Genes

In comparison to the classical HLA class Ia molecules, HLA-E, HLA-F, and HLA-G genes and proteins show very limited polymorphism, and their expression is limited to particular cells and tissues [8, 9] (Fig. 33.2). Although the protein products of these genes bind a limited, but still diverse, set of peptides, their primary role is probably in modulating immune functions through direct interaction with several receptors on diverse subsets of immune cells [8, 9]. The tolerogenic properties of HLA class Ib molecules, and especially the immunosuppressive role of the HLA-G protein, were initially discovered in relation to feto-maternal tolerance and proved important in relation to a successful pregnancy.

HLA-E has the rather unique property of presenting leader sequences from other MHC class I molecules and is recognized by the innate immune receptor CD94/NKG2A expressed predominantly on natural killer (NK) cells and a small subset of T-cells from peripheral blood. Surface expression of HLA-E can protect target cells from lysis by CD94/NKG2A+ NK cell clones.

HLA-F is considered to be the progenitor of modern human MHC class I HLA genes [10]. Unlike class Ia molecules, HLA-F has an intracytoplasmic domain. It is expressed mainly in lymphoid tissue and T- and B-cells, with a lower expression in the spleen and the skin. There is increased expression of HLA-F genes during the last trimester of pregnancy, unlike HLA-G, which is expressed during the totality of pregnancy. At this point, it is not clear whether HLA-F associates with β2-microglobulin or binds peptides. In fact, current evidence suggests that HLA-F exists as an open conformer without β2-microglobulin or peptide that acts as a ligand for NK cell receptors such as KIR3DS1 [11].

HLA-G is primarily expressed on fetal-derived placental cells, although its expression has been shown in other milieus. The tolerogenic properties of HLA class Ib molecules, and especially the immunosuppressive role of the HLA-G protein, were initially discovered in relation to feto-maternal tolerance and proved important in relation to a successful pregnancy. The primary function of HLA-G is that of an immune checkpoint molecule, inhibiting the activity of several cells of the immune system. Membrane-bound or soluble HLA-G strongly binds its inhibitory receptors on NK cells, T-cells, B-cells, monocytes, and dendritic cells and serves an inhibitory function. HLA-G function may therefore be beneficial because when expressed by a fetus or a tissue transplant, it protects them from rejection or deleterious when expressed by a tumor. HLA-G expression can be stress induced and plays important roles in cancer [12], parasitic diseases [13], and transplant immunology [14].

MHC Class I HLA Pseudogenes and Gene Fragments

Since 1992, the existence of multiple other HLA class I genes has been known [15], including the pseudogenes designated HLA-H, HLA-J, HLA-K, and HLA-N (Fig. 33.2). However, sequencing studies have demonstrated the presence of deleterious mutations in these genes which prevent them from being active in antigen presentation or even expressed at the protein level. Evolutionary relationships as assessed by construction of trees suggest the four modern loci, HLA-A, HLA-G, HLA-H, and HLA-J, were formed by successive duplications from a common ancestral gene [11, 15]. In this scheme, one intermediate locus gave rise to HLA-A and HLA-H and the other to HLA-G

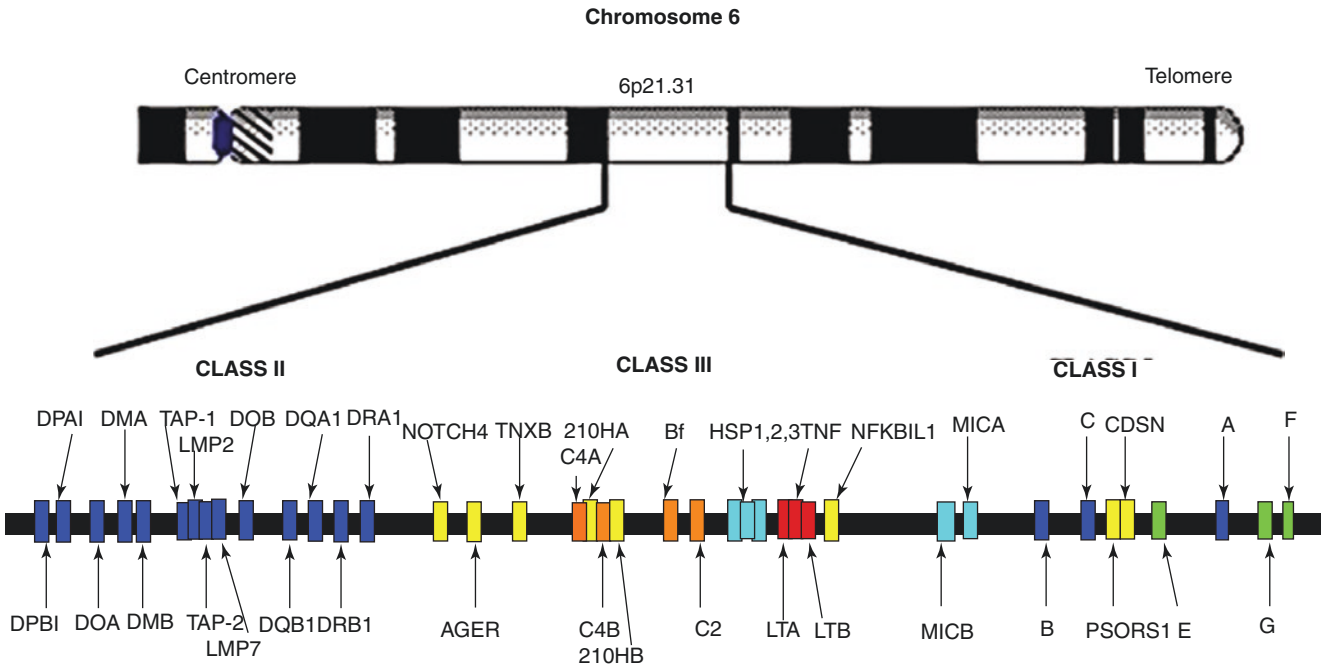

Fig. 33.1 Schematic of the MHC. The 3.6 Mb MHC contains over 220 genes and is divided into three classes. The location of genes involved in antigen processing or presentation is shown in blue, and "nonclassical" HLA genes (HLA-E, -F and -G) are shown in green. Early components of the complement cascade (C4, C2, properdin factor B) are shown in orange. Genes involved in stress responses (HSP1, HSP2, and HSP3; MICA and MICB) are shown in turquoise. The tumor necrosis factor group of genes (LTA, TNF, and LTB) is shown in red. Other genes, such as NOTCH 4, AGER, TNXB, 21-OH-A and 21-OH-B, PSORS1, and CDSN, are shown in yellow. (From Reveille [141]. Reprinted with permission from Springer Nature)

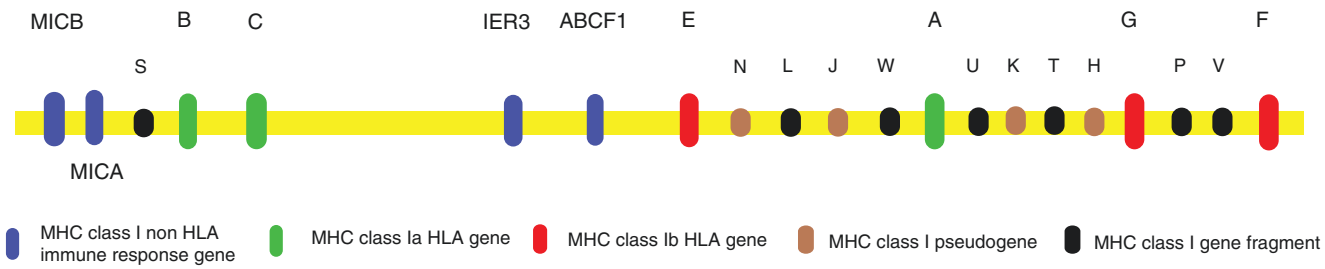

Fig. 33.2 HLA and other immune response genes in the MHC class I region

and HLA-J. Beyond these genes are MHC class I gene fragments designated HLA-L, HLA-P, HLA-S, HLA-T, HLA-U, HLA-V, HLA-W, HLA-Y, and, in the MHC class II region, HLA-Z [16–19].

Non-HLA Immune Response Genes in the Class I MHC Region

MICA and MICB

The major histocompatibility complex class I polypeptide-related sequence A and B genes (MICA and MICB) encode a membrane-bound protein acting as a ligand to stimulate an activating receptor, NKG2D, expressed on the surface of essentially all human natural killer (NK), γδ-T-, and CD8(+) αβ-T-cells [20] and highly expressed in intestinal epithelium. Upon binding to MICA, NKG2D activates cytolytic responses of NK and γδ-T-cells against infected and tumor cells expressing MICA. Therefore, membrane-bound MICA acts as a signal during the early immune response against infection (especially viral) or spontaneously arising tumors. On the other hand, the proteolytic cleavage of MICA proteins from expressing cells, termed as MICA shedding, produces soluble MICA that may control the immune process by downmodulating NKG2D expression and facilitate expansion of an immunosuppressive CD4+ T-cell subset. In addition, MICA can be excreted in exosomes which can also downregulate NKG2D activity [21]. It was reported that *MICA∗008* generated protein was preferentially released from cells in exosomal form [21]. Therefore, the balance between membrane-bound MICA

and soluble MICA/exosomal MICA may control the outcome of immune function via NKG2D regulation. At current, there are 107 recognized MICA alleles coding for 82 proteins and 47 MICB alleles coding for 30 proteins.

The Immune Early Response Gene

Located between HLA-C and HLA-E, the immune early response (IER) gene product functions in the protection of cells from Fas- or tumor necrosis factor-alpha-induced apoptosis [22]. Partially degraded and unspliced transcripts are found after virus infection in vitro, but these transcripts are not found in vivo and do not generate a valid protein.

ATP-Binding Cassette Subfamily F Member 1 (ABCF1)

ABCF1 is an E2 ubiquitin-conjugating enzyme that regulates macrophage function from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype by promoting TLR4 endocytosis and activation of TRIF-dependent signaling [23]. ABC transporter family protein that has been shown to regulate innate immune response is a risk gene for autoimmune pancreatitis and rheumatoid arthritis. Unlike other members of ABC transporter family, ABCF1 lacks transmembrane domains and is thought to function in translation initiation through an interaction with eukaryotic translation initiation factor 2 (eIF2).

MHC Class II Region (Fig. 33.3)

HLA-DR Subregion

The MHC class II HLA-DR molecule is a heterodimer consisting of an alpha (DRA) and a beta chain (DRB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. HLA-DR molecules are expressed in antigen-presenting cells (APC: B-lymphocytes, dendritic cells, macrophages). Within the DR molecule, the beta chain contains all the polymorphisms specifying the peptide-binding specificities. Over alleles, 2444 HLA-DRB1 alleles have been described encoding over 1741 different DRB1 chain allotypes. HLA-DRB1 is present in all individuals and is expressed five times higher than other DRB genes that produce beta chains (DRB3, DRB4, and DRB5) [24]. Different alleles of DRB1 are linked with either none or one of the genes DRB3 (found only on *HLA-DRB1∗03-*, *DRB1∗11-*, *DRB1∗12-*, *DRB1∗13-*, and *DRB1∗14*-bearing haplotypes) (Fig. 33.4), DRB4 (found only on *DRB1∗04-*, *DRB1∗07-*, and *DRB1∗09*-bearing haplotypes), and DRB5 (found only on *HLA-DRB1∗15-* and *DRB1∗16*-bearing haplotypes). *HLA-DRB1∗08* haplotypes are unique as they appear to have resulted from a gene contraction/deletion event. There are four related pseudogenes (DRB2, DRB6, DRB7, DRB8, and DRB9) whose presence varies on different DRB1 haplotypes (Fig. 33.4). HLA-DRB1 is the most polymorphic locus in the MHC class II region and has been implicated in a variety of autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, type I diabetes mellitus, autoimmune thyroid disease, and multiple sclerosis), infectious diseases (leprosy), and other diseases (narcolepsy) [25].

The HLA-DQ Subregion

HLA-DQ belongs to the HLA class II beta chain paralogs. Like HLA-DR, HLA-DQ is a heterodimer consisting of an alpha (DQA) and a beta chain (DQB), both anchored in the membrane. Like HLA-DR, it plays a central role in the immune system by presenting peptides derived from extracellular proteins to the same system of antigen-presenting cells and has the same genetic organization, with greater polymorphism in the DQB chain. Located centromeric to HLA-DQA1 and HLA-DQB1, the DQA2, DQB2, and DQB3 loci represent gene duplication events, although whether they actually express cell surface proteins is unclear [26].

The HLA-DP Subregion

The DP subregion of the HLA class II region contains genes encoding the alpha and beta chains of a heterodimeric, cell surface glycoprotein that presents antigens to CD4+ (helper) T-lymphocytes [26]. HLA-DPA1 is much less polymorphic; indeed, the HLA-DPB1 gene is the third most polymorphic gene in the MHC class II region, with 1312 alleles giving rise to 868 different allotypic beta chains. HLA-DPB1 alleles have been implicated in chronic berylliosis [27], as well as in the topoisomerase I response in systemic sclerosis, juvenile

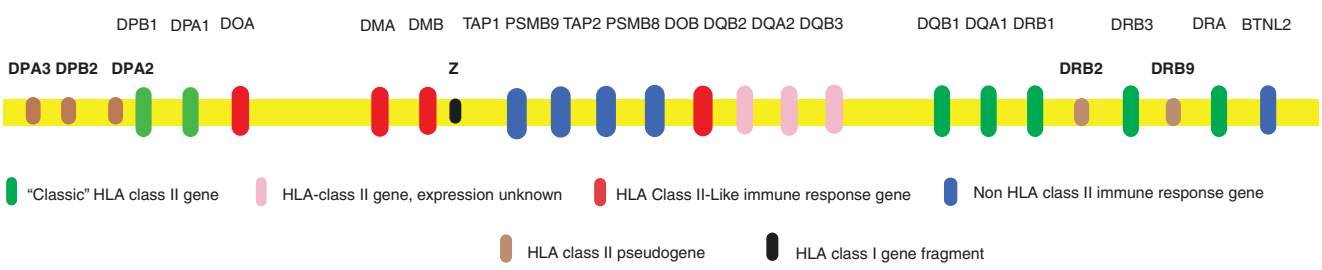

Fig. 33.3 HLA and other immune response genes in the MHC class II region

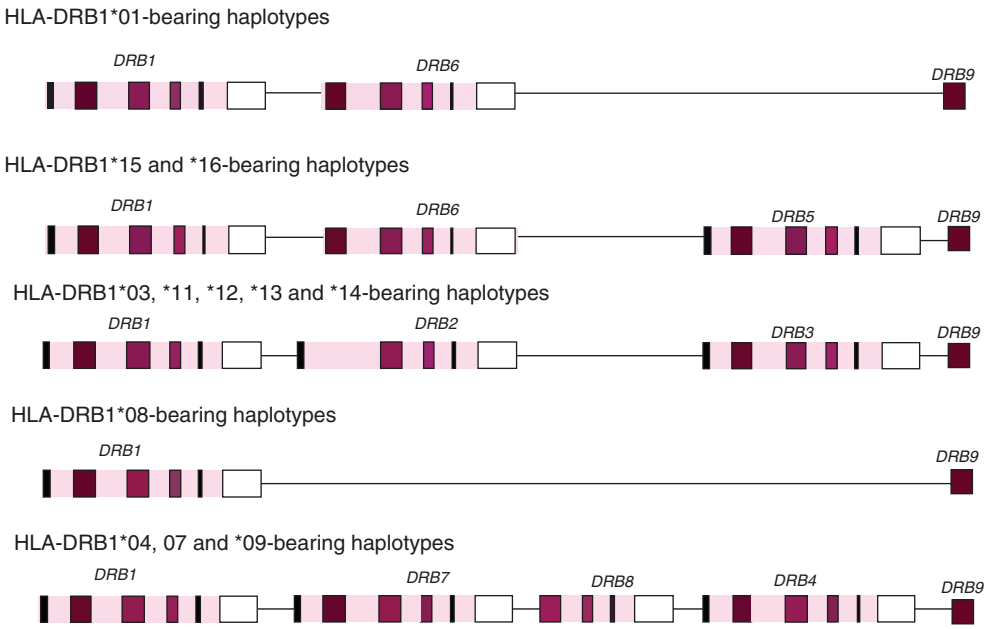

Fig. 33.4 The organization of genes and pseudogenes in the HLA-DR subregion differs by DRB1 haplotype

idiopathic arthritis, and spondyloarthritis. Also found here are pseudogenes HLA-DPA2, HLA-DPA3, and HLA-DPB2 (Fig. 33.3).

Non-HLA Immune Response Genes in the MHC Class II Region

Butyrophilin-Like Protein, Major Histocompatibility Complex Class II Associated (BTNL2)

BTNL2 encodes a major histocompatibility complex class II-associated, type I transmembrane protein which belongs to the butyrophilin-like B7 family of immunoregulators [28]. It is thought to be involved in immune surveillance, serving as a negative T-cell regulator by decreasing T-cell proliferation and cytokine release. The encoded protein contains an N-terminal signal peptide, two pairs of immunoglobulin (Ig)-like domains separated by a heptad peptide sequence, and a C-terminal transmembrane domain. Naturally occurring mutations in this gene are associated with sarcoidosis, rheumatoid arthritis, ulcerative colitis, inflammatory bowel disease, myositis, type I diabetes, systemic lupus erythematosus, acute coronary syndrome, and prostate cancer.

HLA-DM

HLA-DM is a non-polymorphic MHC class II-like molecule that does not bind peptides, but is necessary for the efficient displacement of CLIP from the MHC groove and its exchange for exogenous peptides. HLA-DM senses and interacts with the empty P1 pocket of HLA-DR heterodimers and induces conformational changes that disrupt bonds between the peptide and the binding groove, leading to dissociation of the bound peptide [29]. Removal of the bound peptide generates a receptive conformation that can readily scan suitable stretches of partially folded antigens or large antigenic fragments. This process continues until an optimal peptide is selected from the denatured protein antigen for further trimming and presentation to specific T-cells. Hence, in addition to the removal of CLIP, HLA-DM helps in the selection of immunodominant epitopes.

HLA-DOA and HLA-DOB

HLA-DO is a nonclassical MHC class II-like molecule which is an α/β-heterodimer encoded by the DOA and DOB genes that does not bind peptide [30]. The current understanding about HLA-DO can be distilled into two working hypotheses. In one model, HLA-DO forms a tight complex with HLA-DM in order to prevent HLA-DM from removing the invariant chain peptide CLIP; and in the other, HLA-DO differentially affects the presentation of structurally diverse peptides and acts as a second chaperone together with HLA-DM to fine-tune MHC class II repertoire selection.

Transporter Associated with Antigen Processing (TAP)

Peptides presented to CD8 cytotoxic T-cells (CTLs) by MHC class I proteins are generated by constant turnover of proteins by proteasomes in the cytosol. The peptides generated by the proteasomes are transported into the endoplasmic reticulum (ER) by TAP genes [31]. The TAP heterodimer is composed of TAP1 (ABCB2) and TAP2 (ABCB3), members of the ATP-binding cassette (ABC) family. In the ER, TAP and other proteins of the MHC class I peptide-loading complex (PLC) promote folding of MHC I molecules and ensure proper loading of peptides into the MHC class I

peptide-binding groove. Upon stable peptide loading, the peptide-MHC class I complex is translocated to the cell surface, where it displays the peptides to CD8+ CTLs.

Low-Molecular-Weight Proteasome Genes (PSMB8 and PSMB9)

The immunoproteasome, a distinct class of proteasome found predominantly in monocytes and lymphocytes, shapes the antigenic repertoire presented on major histocompatibility complex (MHC) class I molecules. PSMB8 (previously known as LMP7) and PSMB9 (formerly known as LMP2) function to amplify specific endopeptidase activities of the proteasome. An essential function of a modified proteasome, the immunoproteasome, is the processing of class I MHC peptides [32].

The MHC Class III Region (Fig. 33.5)

Advanced Glycation End Product-Specific Receptor (AGER or RAGE)

This is a member of the immunoglobulin superfamily. It is a multiligand cell surface receptor. AGER principally binds AGEs (produced through glycation of proteins or lipids after sugar exposure), a polypeptide linked with neuronal growth (high-mobility group protein 1 (HMGB1) or amphoterin), and members from the S100 family (S100A8, S100A9, S100A11, S100A12, and S100B) [33]. AGER activation after ligand binding increases receptor expression and activation of pro-inflammatory and procoagulatory pathways, leading, for example, to vascular dysfunction. Several phosphoproteins (NFκB, Akt, p38, and MAP kinases) and adaptors (MyD88, TIRAP, Dock7, and DIAPH-1) are involved in AGER-associated intracellular pathways. AGER is involved in inflammatory and immune responses and causes an unfavorable pro-inflammatory state implicated in multiple pathways and inflammatory diseases, rheumatic or autoimmune diseases, as well as infectious diseases, diabetes, metabolic syndrome and its complications, obesity, insulin resistance, hypertension, atherosclerosis, neurological diseases such as Alzheimer's disease, cardiovascular diseases, pulmonary diseases such as chronic obstructive pulmonary disease (COPD), and cancer [33].

FK506-Binding Protein-Like (FKBPL)

FKBPL, a member of the immunophilin protein family, is a potent secreted antiangiogenic protein targeting the CD44 pathway [34] with a ubiquitous expression in the skin. It functions in immunoregulation and basic cellular processes involving protein folding and trafficking. The encoded protein plays an important role in angiogenesis and appears to have some involvement in the control of the cell cycle.

The Early Components of the Complement Cascade

Complement components 2 (C2) and 4 (C4) represent early steps in the classical complement activation cascade and factor B (Bf) in the "properdin" pathway. C2 and factor B represent gene duplication events, and C2 shows 39% identity with the functionally analogous complement factor B [35]. The copy number of C4 genes in a diploid human genome (i.e., the gene dosage) predominantly varies from two to six in the white population [36, 37]. Each of these genes encodes a C4A or C4B protein. C4 is a constituent of the four-gene module termed the "RCCX," which takes its designation from RP1 (see STK19; 604977), C4, CYP21, and tenascin-XB (TNXB), a glycoprotein of the extracellular matrix predominantly located in the outer reticular lamina of the basement membrane associated with Ehlers-Danlos type I and vesicoureteral reflux 8 syndrome. The C4B isotype of C4 displays three- to fourfold greater hemolytic activity than does the C4A isotype.

Heat Shock 70 Proteins HSP70A, HSP70B, and HSP70L

These duplicated intronless genes encode a 70 kDa heat shock protein which is a member of the heat shock protein 70 family. In conjunction with other heat shock proteins, this protein stabilizes existing proteins against aggregation and mediates the folding of newly translated proteins in the cytosol and in organelles. It is also involved in the ubiquitin-proteasome pathway through interaction with the AU-rich element RNA-binding protein 1 [38].

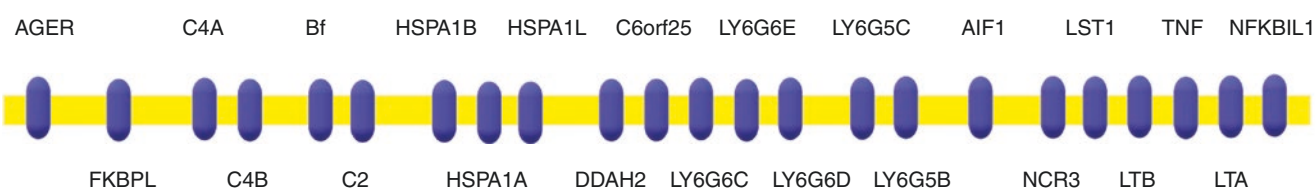

Fig. 33.5 Immune response genes in the MHC class III region

Dimethylarginine Dimethylaminohydrolase 2 (DDAH2)

This gene encodes a dimethylarginine dimethylaminohydrolase. The encoded enzyme functions in nitric oxide generation by regulating the cellular concentrations of methylarginines, which in turn inhibit nitric oxide synthase activity. The protein may be localized to the mitochondria. DDAH2 has been implicated in preeclampsia, sepsis, and renal, pulmonary, and cardiovascular diseases [39].

Megakaryocyte and Platelet Inhibitory Receptor G6b (MPIG6B or C6orf25)

This gene is a member of the immunoglobulin (Ig) superfamily and is located in the major histocompatibility complex (MHC) class III region. The protein encoded by this gene is a glycosylated, plasma membrane-bound cell surface receptor, but soluble isoforms encoded by some transcript variants have been found in the endoplasmic reticulum and Golgi before being secreted [40].

Lymphocyte Antigen 6 (LY6) Family Members LY6G5B, LY6G5C, LY6G6D, and LY6G6E [41]

The LY6 genes are located in the MHC class III region. Members of the LY6 superfamily typically contain 70–80 amino acids, including 8–10 cysteines. Most LY6 proteins are attached to the cell surface by a glycosylphosphatidylinositol (GPI) anchor that is directly involved in signal transduction. These represent 18% of the human Ly6 protein family and 50% of the secreted ones [41].

Allograft Inflammatory Factor-1 (AIF-1) [42]

This is a 17 kDa cytoplasmic, calcium-binding, inflammation-responsive scaffold protein that is mainly expressed in immunocytes. AIF-1 influences the immune system at several key points and thus modulates inflammatory diseases. AIF-1 boosts the expression of inflammatory mediators such as cytokines, chemokines, and inducible nitric oxide synthase (iNOS) and promotes inflammatory cell proliferation and migration [42].

Natural Cytotoxicity Triggering Receptor 3 (NCR3) [43]

NCRs have classically been defined as activating receptors that trigger cytotoxicity and cytokine responses by NK cells upon engaging with ligands on tumor cells. The encoded protein interacts with CD3-zeta (CD247), a T-cell receptor [43]. A single-nucleotide polymorphism in the 5′ untranslated region of this gene has been associated with mild malaria susceptibility.

Leukocyte-Specific Transcript 1(LST1) [44]

The protein encoded by this gene is a membrane protein that can inhibit the proliferation of lymphocytes [44]. Expression of this gene is enhanced by lipopolysaccharide, interferon-gamma, and bacteria. Recent data suggest that LST1 acts as a transmembrane adaptor protein with inhibitory signal transduction and as a membrane scaffold facilitating the formation of tunneling nanotubes.

Lymphotoxin-Alpha and Lymphotoxin-Beta (LTA and LTB) [45]

LTA and LTB encode proteins that are members of the tumor necrosis factor family. LTA is highly inducible and secreted and forms heterotrimers with LTB which anchor LTA to the cell surface. This protein also mediates a large variety of inflammatory, immunostimulatory, and antiviral responses, is involved in the formation of secondary lymphoid organs during development, and plays a role in apoptosis [45]. Genetic variations in this gene are associated with susceptibility to leprosy, myocardial infarction, non-Hodgkin's lymphoma, and psoriatic arthritis (PsA). The predominant form of the LTA/LTB complex on the lymphocyte surface is the LTA1/LTB2 complex, which is the primary ligand for the lymphotoxin-beta receptor.

Tumor Necrosis Factor (TNF)

This gene encodes a multifunctional pro-inflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily [46]. This cytokine is mainly secreted by macrophages. It can bind to and thus functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. This cytokine is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. This cytokine has been implicated in a variety of diseases, including immune-mediated and autoimmune diseases, insulin resistance, and cancer.

NFκB Inhibitor-Like 1 (NFκBIL1) [47]

This gene encodes a divergent member of the I-kappa-B family of proteins. NFκBIL1 is important in the regulation of the NFκB pathway and has been implicated in the pathogenesis of rheumatoid arthritis, inflammatory myopathy, psoriasis, ulcerative colitis (association with the severe type), and systemic lupus erythematosus.

MHC Genes and Spondyloarthritis

HLA-B27

Over 45 years have passed since the original description of the association of HLA-B27 with reactive arthritis [1]. Even to this day, the association of HLA-B27 and spondyloarthritis remains one of the best examples of a disease association with a hereditary marker. In fact, the prevalence

of spondyloarthritis in general and reactive arthritis in particular corresponds to the population frequency of HLA-B27, with the highest frequencies in populations with high prevalence of HLA-B27 and the lowest in populations where HLA-B27 is rare (see in the following).

The Evolution of HLA-B27

There are to date 187 different alleles of HLA-B27 (https://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/allele.cgi) that result in different proteins being produced, including two subtypes (*HLA-B∗27:59*, *HLA-B∗27:64*) whose gene was truncated and did not result in an expressed protein product. Another, *HLA-B∗27:22*, was found to be a sequencing error and is not counted as an allele of HLA-B∗27. Of these, by far the most common is *HLA-B∗27:05*, which has a worldwide distribution and is likely the initial HLA-B∗27 allele, evolving before *Homo sapiens* left Africa (Fig. 33.6). The major subtypes of HLA-B27 include *HLA-B∗27:02*, found in Europe around the Mediterranean Sea; *HLA-B∗27:04*, a common subtype in eastern Asia; *HLA-B∗27:06*, which likely evolved from *HLA-B∗27:04* and is most frequently found in Southeast Asia; and *HLA-B∗27:07*, found in central and near western Asia. *HLA-B∗27:03* is unique to western Africa and *HLA-B∗27:09* to Sardinia and Italy. The other HLA-B27 subtypes are rare and evolved from the major subtypes of HLA-B27 (Fig. 33.7). Most subtypes are derived from either the ubiquitous parent allele *HLA-B∗27:05* or B27 subtypes common in the same geographic region. These geographic regional differences are not as easy to explain in certain situations, for example, why certain HLA-B27 subtypes that appear to be derived from more common "parent" subtypes have been located in ethnic groups far distant, such as *HLA-B∗27:20*, described in individuals in Japan and Korea that appears to be related to *HLA-B∗27:07*, found in western and southern Asia, or *HLA-B∗27:40*, *HLA-B∗27:42*, and *HLA-B∗27:44*, found in China and Taiwan, which appear derived from *HLA-B∗27:08*, found in the United Kingdom, is not clear. Whether this represents a prehistoric migration, or more recent gene admixture, perhaps an independent mutation, is not clear. Still, the most common subtypes associated with spondyloarthritis worldwide are *HLA-B∗27:05* overall; *HLA-B∗27:02* in Europe, North and South America, North Africa, western Asia, and the Middle East; and *HLA-B∗27:04* in eastern and southern Asia.

HLA-B27 and Infection

HLA-B27-restricted cytotoxic T-lymphocyte (CTL) responses to viruses are often tightly focused, resulting in immunodominant responses to small numbers of epitopes. In HIV infection, viral mutation leading to loss of CTL recognition is consistently associated with disease progression, providing strong evidence for a key role of CTL in viral control [48–50]. Among the other genetic factors studied regarding HIV-1 outcome, the major histocompatibility complex (MHC) has been most extensively studied in case-control studies (reviewed in [48, 49]), including those associated with

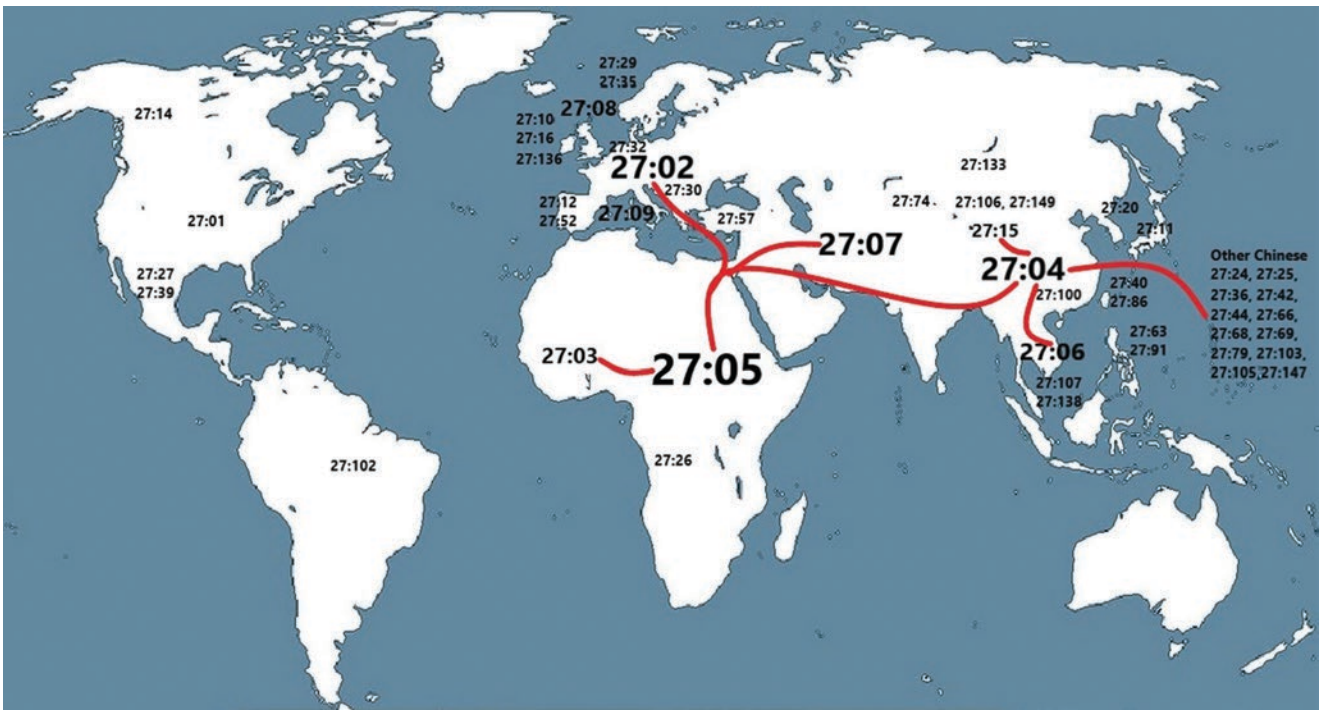

Fig. 33.6 HLA-B27 subtype origins

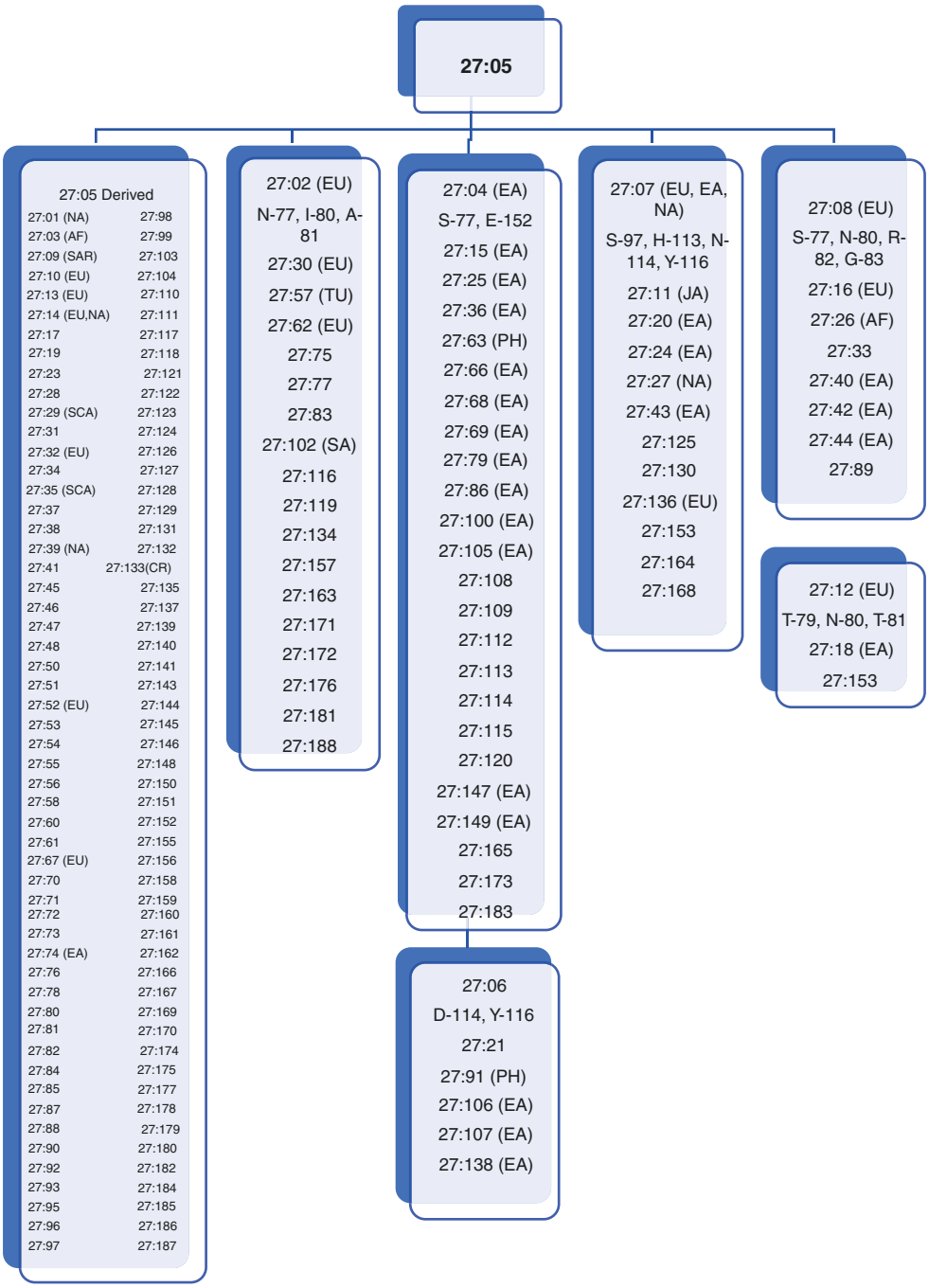

Fig. 33.7 HLA-B27 subtype derivations

slowed disease progression (the HLA-Bw4 family of alleles, most notably *HLA-B∗57*, *HLA-B∗27*, *HLA-B∗51*, *HLA-B∗58:01*, *HLA-B∗13*, *HLA-B∗81:01*, as well as *HLA-DRB1∗13* and possibly *HLA-DRB1∗01*), as well as those associated with accelerated disease progression (HLA class I homozygosity, certain *HLA-B∗35* alleles such as *HLA-B∗35:02* and *HLA-B∗35:03* but not *HLA-B∗35:01*, as well as *HLA-B∗38:02*, *HLA-B∗40:01*, *HLA-B∗50:01*, *HLA-B∗55:01*, and *HLA-DRB1∗15:03*). These associations relate to polymorphisms in the amino acids forming the peptide-binding groove of the HLA molecule involved in direct interaction with the peptide bound. HLA-B∗57 has been shown to have broad reactivity across multiple conserved gag epitopes and reduced fitness of HIV-1-1 escape mutation variants [6]. On the other hand, HLA-B27 presents a conserved immunodominant gag epitope that requires a complex pattern of mutation for escape. Other protective alleles are associated with strong CTL response to gag epitopes or, in the case of *HLA-B∗81:01*, lower replication capacity of escape variants. HLA-B27 also confers immunity in hepatitis C infection, promoting a spontaneous CD8+ T-cell-mediated viral clearance of HCV [50]. It is also of note that the prevalence of HLA-B27 is lowest in

regions of the world where the prevalence of malaria, an intracellular parasite, is highest, leading to speculation that it may confer a survival disadvantage in the face of malaria infection [51].

HLA-B27 and Spondyloarthritis

HLA-B27 has been associated with reactive arthritis worldwide; and in fact SpA and reactive arthritis are highest in frequency in populations where the frequency of HLA-B27 is highest, such as in Eskimos [52, 53] and Native Americans in the second wave (NaDene) of migration, such as the Haida and Navajos [54, 55], and lowest in the Middle East [56–58] and Africa [59, 60]. As far as HLA-B27 subtypes are concerned, *HLA-B∗27:05* and *HLA-B∗27:02* are seen in whites, Eskimos, and Latin Americans [53, 61] and *HLA-B∗27:04* in eastern Asians. On the other hand, certain HLA-B27 subtypes are non-disease associated, specifically *HLA-B∗27:06* (most commonly encountered in Southeast Asia) and HLA-*B∗27:09*, found in Sardinia (primarily). The molecular basis of this lack of disease association is unclear. HLA-B∗27:06 and HLA-B∗27:09 importantly share a tyrosine residue at position 116, not found in the "common" SpA-associated subtypes (*HLA-B∗27:05*, *HLA-B∗27:02*, and *HLA-B∗27:04*). However, this amino acid association is also seen with *HLA-B∗27:07*, which is SpA associated. HLA-B27 positivity has been associated with chronicity of symptoms [62]. In one interesting study [63], patients with positive fecal culture for *Salmonella*, *Campylobacter*, *Yersinia*, *Shigella*, and *E. coli* were addressed by questionnaires inquiring about gastrointestinal symptoms and the occurrence of joint pain in a previously healthy joint within 4 weeks after onset of infection. A significant association between joint pain beginning within 4 weeks of infection and HLA-B27 was found for *Salmonella*, *Shigella*, and *Yersinia*, not, however, for *Campylobacter* and *E. coli*; and a significant association between HLA-B27 and severity of joint pain was observed.

The Role of HLA-B27 in ReA Pathogenesis

The exact mechanism underlying the effect of HLA-B27 on disease susceptibility still has not been determined. To detail all the investigations of HLA and causation of SpA is outside the scope of this chapter and is covered in part in other chapters in this book as well as in recent reviews [2–5]. Five different theories for the role of HLA-B27 in influencing susceptibility to spondyloarthritis have been proposed:

Presentation of an Arthritogenic Peptide

As an MHC class I protein, the "classical" function of HLA-B27 is to present endogenous (i.e., viral, bacterial, tumor, self) peptides that have been degraded intracellularly in proteasomes to the αβ-T-cell antigen receptor on cytotoxic (CD8-positive) T-lymphocytes. However, in addition to their classical antigen-presenting role, HLA class I proteins (and the peptides presented therein) are recognized by members of the killer immunoglobulin receptor (KIR) family on natural killer cells. The HLA-B27 heavy chain is transcribed off of ribosomes in macrophages and retained in the endoplasmic reticulum (ER) by the molecular chaperones calnexin, calreticulin, and oxidoreductase ERp57, the latter a protein disulfide isomerase that reduces and oxidizes disulfide bonds. Then, it is folded into its tertiary structure and bound to β2-microglobulin, after which calnexin releases the complex and the dimer is associated with calreticulin, which in turn chaperones the formation of the peptide loading onto the complex of heavy chain, β2-microglobulin, and antigenic peptide, via the TAP proteins and tapasin. The antigenic peptide has been trimmed to optimal length by endoplasmic reticulum-associated aminopeptidases 1 and 2 (ERAP-1 and ERAP-2). Then, the trimolecular peptide complex (HLA-B27 heavy chain, β2-microglobulin, and peptide) travels to the cell surface, where the antigenic peptide is presented either to the αβ-T-cell receptor on CD8-positive T-lymphocytes or to the killer immunoglobulin receptor (KIR) on natural killer (NK) cells. Analysis of the peptides bound by HLA-B27 reveals a strong preference for peptides of 9–11 amino acids in length, which comprise 93% of the peptides examined, with only 2% of peptides being shorter than 9 residues [3]. There is also a preference for peptides that have an *arginine* at position 2, a consequence of "B pocket" specificity.

The *arthritogenic peptide* hypothesis suggests that ReA or other spondyloarthritides result from the ability of HLA-B27 to bind a unique set of antigenic peptides, either bacterial or self-derived. Disease which results from an HLA-B27-restricted cytotoxic T-cell response to this (these) peptide(s) is found only in joints and other affected tissues. Such a peptide could be bound and presented by all disease-associated HLA-B27 subtypes but not by other HLA class I molecules. After initial enthusiasm about molecular mimicry from *Klebsiella* peptides [64] could not be confirmed, identification of HLA-B27-restricted peptides from the *Chlamydia trachomatis* proteome [65–67], as well as from molecular mimicry between endogenous B27 peptides and this and other environmental antigens [66–73], raised this as a potential disease-causing mechanism. An autoantibody cross-reacting with altered self, such as a covalently modified form of HLA-B27, could play a role in initiating or perpetuating disease. Alternatively, $CD8^+$ CTLs that normally recognize foreign peptides presented by HLA-B27 during an infection might cross-react with arthritogenic self-peptides displayed by HLA-B27. Such autoreactive antibodies or CTLs could then mediate chronic inflammation. Peptide binding analyses of disease-associated and non-associated HLA-B27 subtypes produced contradictory results [74–78]. Detailed structural studies comparing *HLA-B∗27:05* and *HLA-B∗27:09* revealed that *HLA-B∗27:05* can display at least one self-peptide in two

different conformations that can be distinguished by $CD8^+$ CTL, while the same self-peptide appeared in only one conformation when crystallized with *HLA-B∗27:09* [74]. This suggested that altered display of a self-peptide ("dual-peptide conformations") might generate autoreactivity [74]. These studies were extended to *HLA-B∗27:04* and *HLA-B∗27:06* (the latter not associated with SpA) crystallized with the same peptide. Contrary to the results with *HLA-B∗27:05* and *HLA-B∗27:09*, the disease-associated *HLA-B∗27:04* subtype displayed only a single peptide conformation, whereas the non-associated *HLA-B∗27:06* subtype exhibited two conformations [75]. In the latter study, the disease-associated subtypes (*HLA-B∗27:04* and *HLA-B∗27:05*) showed significant heavy-chain conformational flexibility, whereas the non-associated subtypes (*HLA-B∗27:06* and *HLA-B∗27:09*) did not show flexibility. A recent analysis of the peptidomes of the eight most common HLA-B27 subtypes found significant overlap in the spectrum of peptides bound suggesting quantitative rather than qualitative differences in peptide repertoires might underlie differential disease association [78]. This led to the identification of 26 peptides presented in lower abundance by *HLA-B∗27:06* and *HLA-B∗27:09* than disease-associated subtypes. This is an interesting observation and provides a tractable list of putative arthritogenic peptides that can be used to search for autoreactive $CD8^+$ T-cells in patients with ankylosing spondylitis [74–78]. The strongest evidence against this theory is that a specific "arthritogenic peptide" has yet to be demonstrated either in ReA or other types of SpA.

Misfolding and ER Stress

Another tendency the HLA-B27 heavy chains have is to misfold in the ER [79–82]. HLA-B27 misfolding within the endoplasmic reticulum, and the accumulation of misfolded B27 heavy chains, results in a process known as ER-associated degradation (ERAD) that degrades misfolded HLA-B27 heavy chains, similar to what occurs with HLA class I heavy chains produced in the absence of β_2-microglobulin or TAP (where misfolding in the ER is more likely to occur). Misfolding activates XBP1 splicing and leads to the upregulation or activation of pro-inflammatory unfolded protein response (UPR) transcription factors (e.g., XBP1s, ATF4, and ATF6α) and downstream target genes including BiP and CHOP (reviewed in [3]). It also exhibits prolonged interactions with misfolded proteins, preventing premature exit from the ER. However, correction of the HLA-B27 folding defect and the UPR in B27 transgenic rats did not affect the presence or severity of the peripheral or axial arthritis, although beneficial effect on the colitis was seen [83].The UPR intersects with innate immune signaling pathways to synergistically upregulate IFN-β and IL-23 and to promote expression of other cytokines in response to toll-like receptor (TLR) agonists.

Another mechanism to eliminate misfolded peptides is by autophagy, a process where cells move unwanted material into vesicles for transport to lysosomes where degradation occurs. Self-association is a unique property of the HLA-B27 molecule. A recent study blocking autophagy flux with bafilomycin resulted in the accumulation of misfolded HLA-B27 dimers and oligomers as well as monomers, which was comparable with the results of blocking endoplasmic reticulum-associated degradation (ERAD) with the proteasome inhibitor bortezomib. HLA-B7 monomers also accumulated after blocking each degradation pathway. Activation of autophagy with rapamycin rapidly eliminated ~50% of misfolded HLA-B27, while folded HLA-B27 or HLA-B7 monomeric heavy chains were minimally affected [84]. This also suggested that manipulation of the autophagy pathway should be further investigated as a potential therapeutic target in spondyloarthritis.

These properties (homodimer formation and misfolding of HLA-B27 heavy chain in the endoplasmic reticulum [ER]) may trigger ER stress signaling pathways in host cell, which in turn may modulate cell signaling in favor of ReA-triggering bacteria [85]. Intracellular impairment of peptide processing or loading into HLA-B27 by viruses or intracellular bacteria can cause a selective impairment of the immune response.

Homodimer Formation

Self-association is a unique property of the HLA-B27 molecule. HLA-B27 heavy chains can form homodimers in vitro that are dependent on disulfide binding through their *cysteine*-67 residues in the extracellular α1 domain [79, 86, 87]. Heavy-chain self-association can either occur through misfolding in the endoplasmic reticulum or self-association of free heavy chains at the cell surface. A unique property of HLA-B27 is that free heavy chains of HLA-B27 can reach the cell surface in the absence of β2-microglobulin and maintain their peptide-binding groove in vitro. Alternative recognition of different forms of HLA-B27 by leukocyte receptors could influence the function of cells from both innate and adaptive immune systems and may indicate a role for various leukocyte populations in SpA [85–87]. Alternatively, HLA-B27 homodimers migrate to the cell surface where they either become antigenic themselves or present peptide to receptors on other inflammatory cells, especially when the cell's antigen-presenting function is impaired.

Alteration of intracellular invasion/killing of arthritogenic organisms may contribute to the cellular basis for ReA, but the molecular basis of the bactericidal pathways in synoviocytes has not been fully resolved. HLA-B27-positive U937 cells kill *Salmonella* less efficiently than controls and show upregulated production of interleukin-10 and, to a lesser extent, tumor necrosis factor (TNF)-alpha [85, 88]. In fact, HLA-B27-associated modulation of cytokine response

profiles may have importance in the pathogenesis of ReA and has been shown to modulate intracellular growth of *Salmonella* mutants and production of cytokines in infected monocytic U937 cells [85, 88–90]. Certain SPI-2 genes in wild-type bacteria suppress *Salmonella* intracellular growth and production of cytokines in infected HLA-B27-transfected cells [91]. HLA-B27-associated modulation of *Salmonella* SPI-2 genes and cytokine production causes intracellular bacterial persistence and may be important in the persistent infection of the bacteria and the pathogenesis of reactive arthritis. HLA-B27-dependent modulation of *Salmonella* gene expression has been shown also to result in not only persistence but also increased *Salmonella* replication in HLA-B27-positive cells [85, 92, 93]. All of this suggests that limiting intracellular growth might be a strategy for persistence of bacteria in host cells, keeping a balance between pathogenic growth and pathogenesis.

Presentation to CD4-Positive T-Cells

HLA-B27 itself and peptides derived therefrom also can act as autoantigens, where either the trimolecular complex presents processed peptide to the αβ-T-cell receptor on CD4-positive T-lymphocytes or free HLA-B27 heavy chains or HLA-B27 homodimers themselves are recognized as antigenic by the T-cell receptor thence or processed antigenic fragments of HLA-B27 are presented to the T-cell receptor of CD4-positive T-lymphocytes, either itself or via presentation by HLA class II (DR, DQ, and DP) heterodimers [94]. In previous years, amino acid homology between HLA-B27 and microbes triggering reactive arthritis supported the concept of *molecular mimicry*, such as has been described for an outer membrane protein YadA of *Yersinia enterocolitica* that shares a linear tetrapeptide with HLA-B27, a cationic outer membrane protein OmpH of *Salmonella typhimurium*, a hexapeptide of *Klebsiella pneumoniae* nitrogenase, and a pentapeptide shared by a *Shigella flexneri* protein and HLA-B27 [72]. However, this has not been widely confirmed.

Interaction with the Microbiome

Subclinical intestinal inflammation occurs in a significant number of patients affected by SpA and is correlated with the severity of spine inflammation [95]. The gut microbiome has recently been shown to influence several HLA-linked diseases. However, the role of HLA-B27 in shaping the gut microbiome has not been previously investigated. One study identified differences in the cecal microbiota of Lewis rats transgenic for HLA-B27 and human β2-microglobulin (hβ2m), and 16S RNA sequencing revealed significant differences between transgenic animals and wild-type animals by principal coordinates analysis. Further analysis of the data set revealed an increase in *Prevotella* bacterial species and a decrease in *Rikenellaceae* relative abundance in the transgenic animals compared to the wild-type animals [96]. Another study of 16S ribosomal RNA gene sequencing from terminal ileum biopsy specimens obtained from patients with recent-onset tumor necrosis factor antagonist-naive AS and from healthy controls showed that the terminal ileum microbial communities in patients with AS differ significantly from those in healthy controls which showed a higher abundance of five families of bacteria, *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*, and a decrease in *Veillonellaceae* and *Prevotellaceae* [97]. These findings were confirmed in another study of 16S ribosomal fecal RNA sequencing, where a significantly increased abundance of *Ruminococcus gnavus* in SpA was seen, as compared with both patients with RA and healthy controls. Of note, significant difference in microbiota composition was also detected between HLA-B27$^+$ and HLA-B27$^-$ healthy control siblings, indicating that the genetic background may influence the microbiota composition [98]. These data all strongly suggest that HLA-B27 (and likely other HLA alleles) may influence the composition of the gut microbiome. In fact, it has been proposed that spondyloarthritis-associated subclinical gut inflammation may be considered the occult engine of the disease [99]. In the gut, the complex interactions between the microbiome and the host immune system, especially HLA-B27, may lead to the alteration of intestinal barriers and to the aberrant activation of innate immune cells. The role of the microbiome per se and gut-related factors in reactive arthritis pathogenesis is discussed in more detail in another chapter in this textbook.

Other HLA-B Genes

HLA-B60 is a serologically defined specificity that correlates at the DNA level with *HLA-B∗40:01*. Several studies have documented a small role for HLA-B60 (B∗40) in susceptibility to SpA [100–107]. One large study of whites, Han Chinese, and blacks was able to confirm the association of *HLA-B∗40:01* with AS in three ethnic groups [105] (Table 33.2).

Table 33.2 MHC genes positively and negatively associated with AS in three ethnic groups

	Whites		Han Chinese		Blacks	
	$N = 1948$		$N = 446$		$N = 67$	
HLA-B	OR	*P*-value	OR	*P*-value	OR	*P*-value
B∗27:05	36.5	$<10^{-375}$	9.2	$<1 \times 10^{-8}$	41.3	$<1 \times 10^{-8}$
B∗27:02	10.9	1×10^{-15}	n.a.	n.a.	n.a.	n.a.
B∗27:04	n.a.	n.a.	22.6	$<1 \times 10^{-8}$	n.a.	n.a.
B∗07:02	0.35	$<1 \times 10^{-8}$	0.06	6×10^{-4}	0.46	0.05
B∗15:00	0.43	$<1 \times 10^{-8}$	0.40	1×10^{-4}	n.a.	n.a.
B∗35:00	0.46	$<1 \times 10^{-8}$	0.03	0.001	0.24	0.02
B∗40:01	1.41	0.008	1.41	0.008	7.5	0.03

Studies of HLA-B alleles in Latin American patients with SpA, including patients with AS, reactive arthritis, and undifferentiated SpA, found associations with HLA-B∗15 [108–110]. This has also been observed in Tunisian patients with undifferentiated SpA. In Africans with SpA, HLA-B27 was less commonly seen; instead, associations with *HLA-B∗14:03* have been reported (a HLA-B∗14 subtype we did not observe in 67 African-American patients with AS and in French SpA families) [60, 111]. The Immunochip study, which imputed HLA alleles, also implicated *HLA-A∗02:01* in susceptibility to this disease independently of HLA-B27 [106].There is substantial evidence that non-B27 major histocompatibility complex (MHC) genes are associated with spondyloarthritis (SpA).

MICA Genes

Given that balance between membrane-bound MICA and soluble MICA/exosomal MICA may control the outcome of immune function via NKG2D regulation and its high expression in gut epithelium, it is tempting to postulate a role of MICA in SpA pathogenesis. One large study of white and Han Chinese AS patients found a highly significant association of two pro-inflammatory alleles of MICA, namely, *MICA∗007* and *MICA∗019*, with AS [112]. However, given the known linkage disequilibrium of these two alleles with *HLA-B∗27:05* and *HLA-B∗27:04*, respectively, a subsequent imputation analysis could confirm this [113]. A more recent study of MICA and natural killer group 2D receptor (NKG2D) polymorphisms in 162 patients with spondyloarthritis and 124 healthy controls found associations of MICA and NKC3 polymorphisms (related to a low NK cell cytotoxic activity) with spondyloarthritis [114]. Thus, a role for MIC genes in SpA pathogenesis is indeed suggested, but more work needs to be done to establish this with surety.

MHC Class II Genes

Earlier data suggested AS and spondyloarthritis in whites to be associated with HLA-DR1, specifically the *HLA-DRB1∗01:01* allele [115–118]. Another HLA-DR1 allele, namely, *HLA-DRB1∗01:03*, was implicated in AS susceptibility by imputation, as well as with enteropathic arthritis in another study. However, more recent studies have suggested this to be explained by an extended HLA-B27 haplotype, thereby reflecting linkage disequilibrium with *HLA-B∗27:05* and not a primary disease association. In fact, in one large study of white HLA-B27-negative patients with AS, no association was seen [105]. No such association has been demonstrated in nonwhites. *HLA-DPB1∗03:01* has been implicated in AS susceptibility in studies of whites by direct HLA typing [105, 119, 120], as well as in studies showing an association of SNPs around the HLA-DPB1 locus recently established by imputation [106, 119].

Studies of Other MHC Genes and AS Susceptibility

Older, small-scale studies have also suggested associations of ReA and SpA with TAP genes [121, 122], low-molecular-weight proteasome (LMP or PSMB) genes in the MHC class II region [123], and anti-TNF genes in the MHC class III region [124, 125]. However, these have not been confirmed in larger cohorts which studied by gene chip analyses and likely reflect linkage disequilibrium with HLA-B or other disease-associated MHC genes.

Psoriatic Arthritis

The association of HLA-B27 with psoriatic spondylitis and peripheral arthritis in whites soon followed that of ankylosing spondylitis in the early 1970s, soon to be followed by the finding of splits of HLA-B16, namely, HLA-B38 initially and eventually HLA-B37 [126–128]. Some other early HLA associations with psoriatic arthritis (PsA), such as with splits of the broad HLA specificity HLA-B17 (namely, HLA-B57 and HLA-B58) and HLA-Cw6 (now known as *HLA-C∗06:02*), eventually were found to be linked to susceptibility to psoriasis per se than PsA [129, 130]. More recent studies utilized large numbers of patients, and gene chip technologies have implicated *HLA-C∗12:03* and HLA-B alleles with amino acid substitutions at position 45 in PsA susceptibility. Some initial studies implicated MICA genes, located next to HLA-B; however, more recent studies have shown that this reflects linkage disequilibrium with HLA-B [131].

A role for genes of the MHC class II subregion has also been described, such as with *HLA-DRB1∗07:01*, though this has not been widely confirmed [132, 133]. Fewer studies exist in nonwhites with psoriasis and PsA. The best reproduced association has been of *HLA-C∗06:02* and *HLA-B∗57* with psoriasis per se [132–134]. Of note was also the implication of HLA-DPB1 and HLA-BTNL2 genes. PsA in Chinese has primarily been linked to *HLA-B∗27* and *HLA-C∗12:01* [135].

In the setting of HIV-1 infection, where the clinical distinction between reactive arthritis and PsA becomes more difficult, HLA-B27 has emerged as a significant risk factor for the development of inflammatory joint involvement [136].

MHC haplotypes have also been implicated in the clinical presentation of PsA. *HLA-B∗27:05* haplotypes have been positively associated with enthesitis, dactylitis, and symmetric sacroiliitis, whereas the *HLA-B∗08:01-C∗07:01* haplotype has been positively associated with joint fusion and deformities, asymmetrical sacroiliitis, and dactylitis.

HLA-C∗06:02 was negatively associated with asymmetrical sacroiliitis. The highest risk of severe PsA was with *HLA-B∗27:05-C∗02*, *HLA-B∗08:01-C∗07:01*, and *HLA-B∗37:01-C∗06:02* haplotypes, but not with the *HLA-B∗27:05-C∗01* or *HLA-B∗57:01-C∗06:02* haplotype [137]. In contrast, *HLA-B∗44*-bearing haplotypes were associated with presence of milder disease. In another very large study, *HLA-C∗06:02* was protective of PsA compared to psoriasis without arthritis, instead predicting younger age at psoriasis onset; in fact, no association of PsA was seen with HLA-C∗06:02 [138].

Conclusions

In reactive arthritis, as in many of the other rheumatic diseases, the MHC is a "prime mover" in pathogenesis, led by the overwhelming influence of HLA-B27. The MHC influences a variety of immune responses, which are now the targets of novel therapies. HLA-B27 in particular plays a variety of potential roles in pathogenesis, likely joined by other MHC factors. Understanding the complexity of this remarkable cassette of genes and their interaction with each other, with non-MHC influences, and with environmental factors is necessary to understand the pathogenesis of reactive arthritis.

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Reactive Arthritis: Animal Models

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Luis R. Espinoza

Considerable progress has occurred in our understanding of spondyloarthritis since this group of disorders was classified by Moll and Wright [1, 2]. Spondyloarthritis comprises a variety of disorders with complex pathophysiology and overlapping clinical features, in which the HLA-B27 antigen is shared by most patients, especially in ankylosing spondylitis (AS). Clinical manifestations observed preferentially involve peripheral and axial joints, but extra-articular manifestations are also present in some members of the group. Clinical manifestations are characterized by a clinical spectrum in which peripheral joint involvement is dominant in early phases such as in reactive arthritis and axial or spinal involvement is preferentially observed in chronic phases, with the prototype being ankylosing spondylitis. In between these extremes, a variety of clinical manifestations are seen in different frequencies including the skin, eye, gastrointestinal tract, genitourinary tract, and entheses [3–6].

Ankylosing spondylitis, psoriatic arthritis, Reiter's disease, intestinal arthropathies, and Behçet's syndrome were initially included among spondyloarthritides [1, 2]; but recent classification criteria introduced by the Assessment of Spondyloarthritis International Society facilitate their classification by considering two major disorders. One includes peripheral spondyloarthritis (SpA) that requires the presence of peripheral arthritis, enthesitis, and/or dactylitis. The second major group includes axial SpA, which requires the presence of back pain for more than 3 months, and includes a subgroup of patients with inflammatory back pain and sacroiliac and/or spine involvement by MRI, so-called non-radiographic SpA [7–9]. It should be stressed that considerable clinical overlap exists among the different members and classification criteria still require further refinement.

A major advancement in our understanding of the pathogenesis of spondyloarthritis occurred in 1973 when two independent groups of investigators first described the presence of HLA-B27 in about 90% of patients with ankylosing spondylitis [10, 11]. What, however, remains to be defined is the exact role of HLA-B27, although several hypotheses have been put forward [12–14].

Despite advances in our understanding of the complex pathogenic events underlying the pathophysiology of spondyloarthritis, no precise knowledge of the distinct pathways operating in its pathogenesis has hampered our ability to develop more precise and distinct classification criteria. Compounding this situation, lack of animal models mimicking the distinct clinical disorders included in the spondyloarthritides has also contributed to slow further advances in the development of better classification criteria. This, however, began to change in 1990 with the landmark study of Hammer et al. who developed an animal model of HLA-B27-associated human disorder [15]. Hammer et al. to investigate the role of B27 in spondyloarthritis developed a HLA-B27-transgenic rat; and rats from one transgenic line spontaneously developed inflammatory disease involving the gastrointestinal tract, peripheral and axial joints, male genital tract, skin, nails, and heart. Since the initial development of this animal model, several other animal models have been described, some occurring spontaneously and others genetically engineered or induced. None of the models, however, is a true representation of the variety of clinical manifestations observed in spondyloarthritis; but some of them closely resemble human spondyloarthritis. Significant progress in our understanding of pathogenic mechanisms including cytokine pathways involved in clinical manifestations, interaction between the host and gut microbiome, and new therapeutic perspectives has occurred because of work with these animal models.

Animal Models

The principal models of spondyloarthritis include HLA-B27-transgenic rats, HLA-B27-transgenic mice, BALB/c ZAP-70 W163C mutation of ZAP-70 (SKG) mice, B10.RIII

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_34

mice in which IL-23 is systemically overexpressed, TNFΔARE mice, DC-specific A20-deficient mice, and gnotobiotic mice [16–19].

Frequently Used Animal Models of Spondyloarthritis

A. **HLA-B27-transgenic rats:**
   - HLA-B27/ human β2-microglobulin (hβ2m)-transgenic Lewis rats (21-H line)
   - HLA-B27/hβ2m-transgenic F344 rats (33-3 line)
   - HLA-B27/hβ2m-transgenic Lewis rats (F1 line)

B. **HLA-B27-transgenic mice:**
   - SpA phenotype in HLA-B27-transgenic mice (ANKANT)
   - Mice overexpressing tumor necrosis factor (TNF)
   - $TNF^{\Delta ARE}$ mice
   - Mice overexpressing the transmembrane form of TNF (tmTNF) (TgA86)

C. **IL-23-dependent mouse models:**
   - IL-23 minicircle DNA (IL-23mc)-induced disease in B10.RIII mice

D. **SKG mouse model:**
   - Curdlan-induced disease in SKG mice
   - SKG *Chlamydia*-induced reactive arthritis

E. **Miscellaneous animal models:**
   - Selective A20-deficient mouse model
   - Gnotobiotic animal models

HLA-B27-Transgenic Rats

HLA-B27 positivity has been clearly demonstrated in about 90% of Caucasians patients with ankylosing spondylitis (AS) and about 40–50% of patients with other forms of spondyloarthritis including psoriatic arthritis, reactive arthritis, and inflammatory bowel disease (IBD), especially Crohn's disease and ulcerative colitis [10–14]. This finding led investigators to develop HLA-B27/human β2-microglobulin (hβ2m) rodent models to replicate clinical manifestations seen in human SpA [15]. Several lines of HLA-B27/hβ2m rat models have been developed, and we will describe a few of them in more detail.

HLA-B27/hβ2m-Transgenic Lewis Rats (21-4H Line)

Hammer et al. were the first group of investigators who introduced the HLA-B27 and human beta-2-microglobulin genes into rats, a species known to be quite susceptible to experimentally induced inflammatory disease [15]. This procedure was performed in Lewis rats and F344 rats. Several of the lines expressing HLA-B2705 and hβ2m genes (150 copies of HLA-B2705 and 90 copies of hβ2m) designated 21-4H (Lewis background), 33-3 (Fisher), and 21-3 (Lewis) developed a spontaneous multisystem inflammatory disorder mimicking the main features of SpA at age 10 weeks. HLA-B27-transgenic rats, both males and females, usually begin with severe diarrhea by 6 and 10 weeks of age, which follows a variable clinical course with progressive deterioration to include perianal ulceration, bloody stools, and cachexia. After a month of diarrhea, arthritis of the hind limbs occurs in the male rats, followed by orchitis, balanitis, and epididymitis, hyperkeratosis of the tail, dystrophy of the nails, alopecia, and folliculitis on ensuing months. These clinical manifestations are quite like those seen in spondyloarthritides including reactive arthritis, psoriatic arthritis, and IBD-associated SpA.

Histopathological examination of the intestinal wall revealed diffuse mononuclear cell infiltration of the lamina propria in the colon and to a lesser extent in the gastric mucosa and small intestine. The synovial membrane of involved peripheral joints was also infiltrated by mononuclear cells, lymphocytes, plasma cells, and neutrophils, as well as the tendons, entheses, bone, and cartilage with the presence of erosions and new bone formation. Inflammatory changes were also observed in other tissues including the sacroiliac and spinal apophyseal joints, heart, eyes, lungs, liver, kidneys, pancreas, spleen, adrenal glands, and thymus. Subsequent published work from the same group revealed that HLA-B27-transgenic rats raised in a germfree environment do not develop inflammatory intestinal or peripheral joint disease, whereas the skin and genital inflammatory lesions are unaffected by the germfree state [20]. These findings provide support for the notion that the gut and joint inflammations are pathogenically closely related, and they provide direct evidence that the commensal gut flora plays an important role in the pathogenesis of HLA-B27-associated gut and joint inflammation.

HLA-B27/hβ2m-Transgenic F344 Rats (33-3 Line)

This transgenic rat line contains only 55 copies of HLA-B2705 and 66 copies of hβ2m and spontaneously developed diarrhea, followed by genital tract involvement, arthritis, and skin/nail lesions. These clinical manifestations, however, appear earlier than in 21-4H rats (at age 6–8 weeks). The histological appearance is also like that seen in the 21-4H rats. At the molecular level, IL-1, IL-2, and IFN-γ were the dominant cytokines expressed in the gut, while TGF-β was overexpressed in the synovium [12, 21].

HLA-B27/hβ2m-Transgenic Lewis Rats (F1 Line)

Tran et al. developed a new HLA-B27-transgenic rat model in which the number of HLA-B27 and hβ2m copies was reversed, aimed at rescuing HLA-B27 heavy chains from misfolding at the endoplasmic reticulum and hoping to ameliorate disease manifestations. To accomplish it, they crossed the 21-3 line with the 283-2 line. The resulting 21-3 line has 20 copies of HLA-B27 and 15 copies of hβ2m and did not develop spontaneous disease, although homozygous 21-3 rats could develop diarrhea, arthritis, and orchitis. The 283-2 line contains only 35 copies of hβ2m transgene and does not develop disease [12].

Of interest, the crossed F1 rats (20 copies of HLA-B27 and 50 copies of hβ2m) exhibited no evidence of gastrointestinal inflammation; but male rats developed epididymo-orchitis at age 3 months, about 70% developed arthritis by the fourth to sixth month, and 30–50% developed spondylitis at a later age, 7–9 months. Orchiectomy prior to the onset of arthritis and spondylitis prevented their appearance [22].

Histopathology revealed inflammatory infiltrate consisting of polymorphonuclear cells localized at the junction of the annulus fibrosus and vertebral bone, which eventually eroded the bony end plate in association with multinucleated giant cells resembling osteoclasts. End-stage disease was characterized by destruction of the intervertebral disk and vertebral body, with persistence of inflammatory infiltrate as well as osteoclastic bone resorption. In addition, new bone formation appeared in the presence of moderate inflammatory changes and persisted during the phases of severe inflammation and end-stage bony destruction [23].

Arthritis on this model was characterized by polymorphonuclear cell infiltration of the synovial membrane, and the inflamed pannus gradually invaded the cartilage and bone. Both synovitis and osteitis were characterized by multinucleated giant cells eroding bone surfaces, with periosteal new bone formation observed at different stages of peripheral arthritis.

The most striking manifestations of this rat model are the pronounced peripheral and axial clinical manifestations, including new bone formation leading to ankyloses, without overt clinical or histologic evidence of GI, skin, or ocular manifestations.

Specificity of the SpA-like spondyloarthritis for the HLA-B27 transgene was established by demonstrating that an HLA-B0702/hβ2m-transgene rat line with several copies and a level of expression of the HLA-27 transgene comparable to the level in disease-prone HLA-27-transgene lines had a normal development [24].

HLA-B27-Transgene Mice

Mice transgenic for HLA-B27 have also become available for investigation, but although these models express a functional HLA-B27 gene product, HLA-B27-transgenic mice usually remain healthy [25, 26].

The transgene expression of human HLA-B27 in murine β2m-deficient mice leads to arthritis of the hind paws in about 75% of males, which eventually evolves into ankyloses in 40% of these mice. Mice also showed hyperkeratotic nails but do not exhibit inflammatory changes in the gut or spine. Histologic analysis demonstrates the presence of synovial hyperplasia and cartilage and bone erosions. Similar clinical manifestations were shown in HLA-B27-transgene mβ2m-deficient mice that express a human β2m transgene, but these findings need further replication.

SpA Phenotype in HLA-B27-Transgene Mice

Murine ANKENT is a progressive ankylosing enthesitis that spontaneously occurs in ankle and/or tarsal joints of aging mice [27]. The term was first used with respect to HLA-B27-transgenic mice on the C57BL/10 background carrying five to ten copies of HLA-B2702 and bearing the B10.BR(H-2k) haplotype. This disorder shares several features with AS, such as MHC- and non-MHC-linked genetic predisposition, male predominance, and inflammatory cell infiltration of entheses. Susceptible mice transgenic for HLA-B2702 develop a higher incidence of spontaneous tarsal joint ankyloses. In addition, development of tarsal ankylosis is highly dependent on the bacterial flora, since its frequency is reduced in specific pathogen-free (SPF) as compared to conventional conditions and it is not observed in mice raised in germ-free conditions.

Tarsal ankylosis is mediated by the presence of cartilage proliferation and subsequent ossification at the bone insertions of the ligaments of joint capsules. No pathologic changes are seen in the spine or in any extra-articular tissue. The prevalence of ankle arthritis is relatively low, at 30% [28, 29].

Clinical swelling may be observed, but the presence of inflammatory infiltrates in the synovium in aging DBA/1 mice cannot be detected. However, histologic examination may show dactylitis and enthesitis in which cell infiltration by polymorphonuclear and mononuclear cells is present. As early as 4 weeks, cartilage hyperplasia develops and gradually progresses to bone formation and eventually joint ankyloses. Dactylitis, tenosynovitis, and onycho-periostitis also occur in this mouse model and are often mimicking peripheral entheseal inflammation and bone formation [30, 31].

Mice Overexpressing Tumor Necrosis Factor (TNF)

TNF plays a major pathogenic role in SpA, especially in the induction of structural joint and bone damage by its ability to activate osteoclasts and inhibit osteoblast [32, 33]. In addi-

tion, its potential role in new bone formation, especially in SpA, remains to be defined. In recent years, to explore the potential role of TNF in new bone formation in SpA, several strains of mice overexpressing TNF have been developed. Most models, however, exhibit clinical manifestations that closely resemble rheumatoid arthritis rather than SpA. Herein, we will describe the most commonly used models in SpA [34, 35].

TNF$^{\Delta ARE}$ Mice

These animal models are characterized by a sustained overexpression of murine TNF secondary to a deletion of 69 bp-long 3' UTR regulatory TNF AU-rich elements (AREs) [35, 36]. At an early age, 4–5 weeks, TNF$^{\Delta ARE}$ mice spontaneously developed an inflammatory disease characterized by chronic peripheral arthritis leading to severe distortion of the front and rear paws and involvement of sacroiliac joints by synovitis, demonstrated by histology and imaging studies. TNF$^{\Delta ARE}$ mice also developed inflammatory bowel disease, which first appears in the terminal ilium and colon at 2–4 weeks. Enthesitis involving the interphalangeal joints, Achilles tendon, and grand trochanter ligaments occurs at 4–8 weeks. Synovial hyperplasia, infiltration by polymorphonuclear cells, pannus formation, and subchondral bone erosions also develop. However, TNF$^{\Delta ARE}$ mice do not exhibit axial involvement and new bone formation. This model closely resembles SpA with histologic evidence of gut inflammation [37].

Mice Overexpressing the Transmembrane Form of TNF (tmTNF) (TgA86)

A transgenic mouse model that specifically overexpressed tmTNF was developed to ascertain the roles of tmTNF and soluble TNF (sTNF) separately. TNF is generated as a transmembrane molecule that when cleaved from the cell surface by TNF-alpha-converting enzyme-like protease (TACE)/ADAM-17 forms soluble TNF (sTNF). Both tmTNF and sTNF are biologically active and signal through TNF receptor type I (TNFRI) and TNFRII [38].

In tmTNF-transgenic mice, peripheral arthritis and spondylitis develop spontaneously at the fourth week in 100% of mice. Arthritis, however, is not as severe and destructive as compared to other TNF-overexpressing models and characteristically affects the front and rear paws with loss of grip strength. Spondylitis also occurs, and it is characterized by a hunchback formation and crinkled tails. As opposed to other TNF-overexpressing models, tmTNF-transgenic mice do not exhibit systemic inflammation.

Histologically, synovitis, enthesitis, and new bone formation are observed. In addition, there is radiological evidence of new bone formation by demonstration of bridging of the tail vertebrae. There is no histologic evidence of inflammatory changes in extra-articular organs [39].

IL-23-Dependent Mouse Models

Genome-wide association studies clearly identified several susceptibility loci in the IL-23/IL-17 pathway including IL-23A, IL-12B, and IL-23R as being strongly associated with AS [40, 41]. And it had been previously shown that mice lacking the IL-23p19 subunit failed to develop collagen-induced arthritis (CIA), a model used to study rheumatoid arthritis [42]. Confirmatory evidence of the involvement of these cytokines in human SpA was provided by phase II and III clinical trials using targeted drug therapies against IL-23, IL-12, IL-17A, and IL-17RA [43, 44].

IL-23 Minicircle DNA (IL-23mc)-Induced Disease in B10.RIII Mice

IL-23-transgenic mice are not viable. Therefore, Adamopoulos et al. used a hydrodynamic method for delivery of IL-23 minicircle DNA encoding IL-23p19 and IL-12p40 (IL-23/IL-12) subunits into B10.RIII hepatocytes and obtained sustained systemic IL-23 expression [45]. This overexpression of IL-23 induced a CD4 T-cell-independent inflammatory response, upregulated by TNF, IL-17A, IL-17F, IL-6, IL-21, IL-22, IFN-γ, and GM-CSF after 4 weeks [45]. Systemic IL-23 expression led to severe and destructive polyarthritis of the paws. Histologic examination revealed hyperplastic synovial pannus with infiltrating mononuclear cells, increased myelopoiesis, osteoclast differentiation, and distinct bone loss and erosions of the cortical bones. However, this model does not exhibit other SpA features such as axial involvement with enthesitis, new bone formation, and extra-articular manifestations. Sherlock et al., however, in a subsequent experiment using the same model, described severe paw swelling as early as 5 days after IL-23mc administration, followed by marked expansion of periosteal osteoblasts along with cortical bone erosions [46]. In addition, the mice also developed psoriasis-like disease and aortic root and valve inflammation, but without evidence of gut, kidney, or liver disease. It was shown that inflammation and osteoproliferation was driven by IL-23-responsive retinoic acid receptor-related orphan nuclear receptor-γt (RORγt)+CD3+CD4-CD8-entheseal resident lymphocytes that were responsive to IL-23 and that produced inflammatory cytokines such as IL-22 and IL-17 [47].

The exact reason for the different clinical phenotypes in these two models remains to be elucidated, but these studies clearly demonstrate that IL-23/IL-17 can drive chronic inflammation and SpA-like disease.

SKG Mouse Model

In 2003, Sakaguchi et al. established a mouse strain, designated SKG mice, which spontaneously develop a rheumatoid arthritis-like inflammatory disorder with formation of pannus eroding the cartilage and bone, presence of rheumatoid factor, and various extra-articular manifestations [48]. The abnormality in this model was found to be expressed in the bone marrow-derived cellular components, leading to thymic generation and activation of CD4+ T-cells recognizing/attacking normal self-antigens in the joints. It was further found that the SKG mouse harbors a point mutation in the ZAP-70 gene yielding reduced T-cell receptor (TCR) signaling, IL-17 dependent, develops multiorgan inflammation under microbial influence, mimics human SpA disease pathogenesis, and is a promising tool for designing new therapies against SpA [48].

Curdlan-Induced Disease in SKG Mice

SKG mice remain healthy under specific pathogen-free (SPF) conditions. But when SKG mice housed in SPF conditions are immunized with the fungal wall component curdlan, they develop arthritis of the ankles and wrists, which is more severe in females, dactylitis, deformities of the tail, and a hunched back [49]. An inflammatory infiltrate appears in the synovium, in intervertebral disks of the spine, and in entheses of the fascia plantaris and Achilles tendon as early as 1 week. Imaging studies confirm the presence of erosions and new bone formation in the spine and interphalangeal joints [50].

Mice also develop extra-articular manifestations including asymptomatic ileitis in 50–60% (at 10–12 weeks after induction), unilateral anterior uveitis in 25%, and atypical skin lesions, but no psoriasis. Systemic involvement is not present, and rheumatoid factor is also absent. These findings provide support for the notion that the IL-23-IL-17 axis plays a role in curdlan-induced disease in the SKG mouse model [51, 52].

Further work with the SKG mouse model has shown microbiota content and response to curdlan varied according to whether T-cell receptor signal strength was normal or was impaired due to ZAP-70(W163C) mutation [53]. Curdlan triggered acute inflammation regardless of the presence of the SKG allele or microbiota. However, no or limited microbiota content attenuated the severity of arthritis. In contrast, ileal IL-23 expression, ER stress, lymph node IL-17 production, goblet cell loss, and ileitis development were microbiota dependent. TLR-4 deficiency induced suppression of ileitis but no arthritis [53].

SKG *Chlamydia*-Induced Reactive Arthritis

Baillet et al. have recently shown that in a susceptible SKG strain, *Chlamydia*-induced reactive arthritis occurs because of deficient intracellular pathogen control, with antigen-specific TNF production upon dissemination of antigen, and TNF-dependent inflammatory disease [54]. They found that the TCR ZAP-70^{w163c} mutation predisposed SKG mice to certain clinical manifestations reminiscent of reactive arthritis, including asymmetric arthritis, enthesitis, spondylitis, sacroiliitis, conjunctivitis, and psoriatic-like skin rash, upon *C. muridarum* infection [54]. Disease phenotypes varied between SKG male and female mice, with a tendency to develop conjunctivitis in males, whereas females had more severe arthritis, spondylitis, and enthesitis. *Chlamydia*-induced reactive arthritis in these animals appears to be driven by altered host immunity to *Chlamydia* rather than self-cross reactivity. Autoantibodies were absent in *C. muridarum*-induced reactive arthritis. T-cell IFN-γ production fails to clear the intracellular pathogen, thereby resulting in a persistent high bacterial load in the genital tract and an elevated TNF levels. Data also suggest that Treg cells in SKG mice restrain TNF production, and in their absence, chlamydial infection triggers TNF-dependent reactive arthritis associated with a reduced rate of bacterial clearance. SKG myeloid cells, presumably macrophages, were found to transport intracellular *Chlamydia muridarum* from the genital tract and to disseminate antigen and PAMPs to distal tissues, thereby inducing inflammation by activating native immune responses. Authors conclude that the inflammatory response in SKG mice may be detrimental to local control of infection and restriction of tissue dissemination of chlamydial antigen and that it is independent of HLA-B27 and sustained by T-cell-specific TNF inflammatory responses in peripheral tissues [54].

Gnotobiotic Animal Models

Gnotobiotic animals are animals in which only certain known bacteria and other microorganisms are present. The term also includes germfree animals. Gnotobiotic animals are born in aseptic conditions, which may include separation from the mother by Caesarean section and immediate transfer of the newborn to an isolator where all incoming air, food, and water

are sterilized. Such animals are reared in a sterile or microbial-controlled laboratory environment, and they are only exposed to those microorganisms that the investigators wish to have present in them. The gnotobiotic animals are used to study the symbiotic relationships between an animal and one or more of the microorganisms that may inhabit its body. Animals reared in a gnotobiotic colony often have poorly developed immune systems, lower cardiac output, abnormal intestinal walls, and high susceptibility to infectious microorganisms. Use of these animals allows the study of selected symbiotic interactions at a time, whereas animals under normal conditions quickly acquire a microbiota that includes thousands of unique microorganisms. Gnotobiotic animals are increasingly being used to study the interrelationship between the host and individual arthritogenic microorganisms [55–57].

What Have We Learned from Animal Models?

The development of animal models of human SpA in the past few decades has improved our understanding of the pathophysiology, clinical characteristics, and design of novel therapeutic modalities. Available animal models, although no one truly resembles the pathophysiology and clinical phenotypes of human SpA, can be used to study relevant and specific aspects of disease.

Information gathered to date has provided important and relevant data on disease pathogenesis including potential mechanisms of how HLA-B27 participates in disease pathogenesis, the role of different cytokine pathways especially of the IL-17/IL-23 axis, cellular elements such as dendritic cells, and development of innovative therapies [58–60]. It can be concluded that SpA in rodent models results from the complex interaction between genetic, environmental (microbiologic), and immunologic predisposing factors in a similar manner to that occurring in humans.

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Reactive Arthritis: Clinical Features and Treatment

35

John D. Carter and Alan P. Hudson

The spondyloarthritides (SpAs) represent a group of inflammatory arthritides that share clinical features. The SpAs have traditionally been divided into five subtypes: ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthritis, reactive arthritis (ReA), and undifferentiated spondyloarthritis. In recent years, some have argued for a paradigm shift regarding the overall classification of the SpAs. Many now suggest that these arthritides would be more accurately divided into axial or peripheral arthritis depending on the focus of their symptoms [1]. Data suggest that this straightforward approach might better associate the shared clinical features and also better define therapeutic strategies. While this chapter will focus on the clinical features and treatment of ReA, it will do so with consideration for axial versus peripheral phenotypes of ReA.

Historical Origins of Reactive Arthritis

Reactive Arthritis is one of the earliest defined types of inflammatory arthritis. It represents the classic interplay between host and environment. ReA is an inflammatory syndrome that develops after certain preceding genitourinary or gastrointestinal infections. Historical medical literature is replete with potential descriptions of ReA, with some more compelling than others. In 1942, the credit for the original description of ReA was given to Hans Reiter by two Harvard researchers (Bauer and Engelman) [2]. Reiter had earlier described the clinical triad of arthritis, nongonococcal urethritis, and conjunctivitis in a German soldier after an episode of bloody diarrhea in 1916 [3]. However, Hippocrates may have been the first to describe ReA in 460 BC, when he made the observation that "a youth does not suffer from gout until sexual intercourse" [4]. At the time, the term "gout" was used indiscriminately as a description for inflammatory arthritis [5]. Several other clinicians described similar cases as well. For example, Pierre van Forest described a case of "secondary arthritis and urethritis" in 1507, Thomas Sydenham's association of arthritis with diarrhea in 1686, Stoll's documentation of arthritis following dysentery in 1776 [6–8], and Fiessinger and Leroy's description of ReA in the same year as Reiter [9]. Perhaps the most articulate description of ReA was by the English physiologist and surgeon Sir Benjamin Brodie in his 1818 treatise "Pathologic and Surgical Observations on the Diseases of the Joints" [10]. His keen observations described five patients with a "train of symptoms" consisting of urethritis, arthritis, and conjunctivitis.

Current State of Reactive Arthritis

Although ReA has been well recognized for several hundred years, recent advances in the understanding of disease pathophysiology, clinical features, and optimized therapeutic strategies have been limited. Remarkably, even though an infectious trigger has been recognized since the beginning, the role that these same etiologic agents might play in disease propagation remains a debate. A specific genetic factor that influences disease susceptibility, HLA-B27, was recognized rather early on, but it remains clear that this HLA locus is not the sole determinant of disease. It might also be that this gene locus predisposes to the "classic triad" of symptoms, a more fulminant presentation and the chronicity of symptoms (described in detail later in this chapter), thereby making the disease more phenotypical apparent potentially creating a diagnostic bias [11]. Because bacterial agents serve as the etiologic trigger of ReA, it is natural to speculate that antibiotics might serve as ideal treatment strategy. However, a rather large amount of clinical trial data has produced apparent conflicting results. Even the most basic of

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_35

principles, disease classification, remains inadequate. The American College of Rheumatology and the Third International Workshop on Reactive Arthritis in 1995, followed by the Fourth International Workshop on Reactive Arthritis in 1999 [12, 13], have outlined diagnostic criteria, but they remain poorly validated and almost universally ignored. This chapter will address these issues and attempt to pave directions for improvement.

Etiologic Agents of ReA

As stated, ReA develops after certain specific bacterial infections of the gastrointestinal or genitourinary tract. The term "reactive arthritis" was first used by Ahvonen, Sievers, and Aho [14] when they described ReA as arthritis, which develops soon after or during infection elsewhere in the body, but in which the microorganism cannot be recovered from the joint. Their description was used to describe post-dysentery ReA in association with enteric infection caused by *Yersinia enterocolitica* [14], but other gram-negative microbes causing enteric infections can also trigger ReA. These include Yersinia, different serovars of *Salmonella enterica*, *Campylobacter jejuni*, *Campylobacter lari*, *Shigella flexneri*, *Shigella sonnei*, and *Shigella dysenteriae* [15–24]. The well-defined urogenital pathogen known to cause ReA is *Chlamydia trachomatis* [18]. There are several other organisms that have been labeled as potential causes of ReA; the two that have the most compelling support are *Chlamydia pneumoniae* [25] and *Clostridium difficile* [19–21].

Diagnosis and Pathophysiology of ReA

ReA occurs after approximately 5% of acute genital *C. trachomatis* infections and 1–15% of gastrointestinal infections with one of the causative organisms [18]. One study suggested that the inciting infection can be detected in about 60% of the ReA patients [26]. However, it is well accepted that the distinct bacterial etiologic agent can remain undetected in many patients. In such cases, it is suggested that the diagnosis be based on clinical features with a supporting history of a typical preceding infection. Indeed, this is a criterion in both of the previously mentioned diagnostic criteria [12, 13]. The antecedent infection could have occurred anywhere from 1 to 4 weeks prior to the onset of the symptoms of ReA. Therefore, 100% of cases require an adequate preceding medical history in order to establish the diagnosis and in approximately 40% of these cases, the triggering bacterial remains undetected. To complicate matters, the 4-week cutoff requirement from the time of the initial infection to the onset of ReA is arbitrary. This timeline was proposed by the Third International Workshop on ReA in 1995 [12]. They acknowledged that the triggering infection could occur 6 weeks, or even longer, prior to the onset of ReA symptoms, but they felt if they extended the timeline in their diagnostic criteria, it might make the criteria less specific. Even worse, because of undetectable triggering infections, the diagnosis cannot even be made using these same diagnostic criteria in some patients with ReA. *Chlamydia trachomatis* is the most common cause of ReA in the USA, and it might be particularly prone to underdiagnosis using these diagnostic criteria. Approximately half of acute genitourinary infections with *C. trachomatis* are asymptomatic. Studies have demonstrated that these asymptomatic *C. trachomatis* infections can cause ReA [18]. Because the diagnostic criteria require a preceding clinical infection, this would render these diagnostic criteria useless in these patients.

It is clear that the triggering etiologic agents are well-defined and our ability to detect them is inadequate. What about the role they play in disease propagation? The answer is even stealthier. The primary focus of infection by these gram-negative lipopolysaccharide-containing bacteria is through mucosal membrane. Common to these microbes is that they are intracellular pathogens. Because there are apparent differences in the pathophysiology of post-chlamydial vs. the post-enteric organisms, these will be discussed separately.

Chlamydia trachomatis (Ct) is a very common pathogen. The CDC estimates three million new *C. trachomatis* infections yearly in the US [27]. Ct has been demonstrated in 50% of patients with a preceding symptomatic urogenital infection who developed ReA [28]. This suggests it is the most common etiologic agent for ReA. The routine presence of Ct has also been demonstrated by polymerase chain reaction (PCR) in the synovial tissue of patients with both acute and chronic ReA [29–31]. Thus, it is well established that these chlamydiae traffic from the initial site of infection to the synovial tissue. Of special interest is the fact that these chlamydiae are viable, but they exist in an aberrant state. These persistently viable chlamydiae have been demonstrated years after the initial infection. The gene regulation is very different in this persistent form of *C. trachomatis* compared to the acute infecting form. These important differences allow it to persist, or harbor, in the synovium and perhaps other tissues (see Chap.1). This downregulated and latent form of the organism might have important implications for treatment that will be discussed later in this chapter.

One of the many unsolved mysteries of ReA, and specifically post-chlamydia ReA, has to do with disease determination. Why do only about 5% of patients with an acute *C. trachomatis* genital infection develop post-chlamydial ReA? Traditional research has focused on the host. More recent data suggest the organism might hold the answer. It is important to note that there are several strains, or serovars, of *Chlamydia trachomatis*. These include both genital and ocular serovars. The assumption has been that since the

arthritis follows genital chlamydial infection, the particular organisms responsible must belong to one of the genital groups. Our group determined the *C. trachomatis* DNA sequence from each of 36 patients with well-defined chronic Chlamydia-induced ReA. We were surprised to find that all cloned samples from each patient were derived from ocular, not genital, strains of the organism [32]. We also assessed a number of other loci that differ in characteristic ways between ocular and genital strains of *C. trachomatis*, and all of them were clearly ocular in structure (see Chap.1). Moving forward, full genome sequencing will be required to definitively determine whether synovial isolates from ReA patients are fully ocular in genetic structure, or whether they are a hybrid of ocular and genital strains. However, these data suggest the ocular strains are uniquely arthritogenic and might have particular tropism for the synovium and possibly other affected organs of ReA.

It should be noted that PCR and RT-PCR data demonstrating chlamydiae in the synovial tissue are not unique to patients with Chlamydia-induced ReA. There have been similar studies demonstrating this same organism in the synovial tissue of a small number of patients with osteoarthritis and even normal controls [33–35]. These data have called into question the importance PCR and RT-PCR findings in patients with Chlamydia-induced ReA. However, the percentage of patients that are positive for *C. trachomatis* in these other studies is significantly less compared to patients with ReA. These other studies have also not attempted to define the specific serovar of *C. trachomatis* discovered in these other patients.

PCR technology has also demonstrated the presence of chromosomal DNA from the known enteric triggers in the synovial tissue of patients with the post-dysentery form of ReA [36, 37]. However, one important difference is that the synovial-based DNA from these post-enteric organisms primarily consists of bacterial DNA fragments and is not metabolically active as is the case with chlamydiae. One possible exception is with Yersinia [38].

Clinical Features

As stated, ReA is a type of SpA. The spectrum of clinical manifestations is shared among the different types of SpA; thus, they are felt to be part of the same family of inflammatory syndromes. However, certain phenotypic features are more common in the different types of SpA. Specifically, ReA shares more phenotypic expression with psoriatic arthritis (PsA), the arthritis associated with inflammatory bowel disease is more similar to ankylosing spondylitis. These characteristics will be discussed. It is also generally felt that the clinical features of post-venereal ReA are congruent with the post-dysentery type; however, most studies assessing the phenotypic expression of ReA lump both variants together so it is difficult to know if there are subtle differences between each subgroup. This chapter will explore some potential differences, especially in the context of axial and peripheral symptoms.

Clinical Manifestations of ReA

Acute Symptoms

Articular

Most commonly present with oligoarthritis, but can also present with polyarthritis or monoarthritis

Axial: *Frequently involved*

- Sacroiliac joints
- Lumbar spine

Occasionally involved

- Thoracic spine (usually seen in chronic ReA)
- Cervical spine (usually seen in chronic ReA)
- Cartilaginous joints (symphysis pubis; sternoclavicular and costosternal joints)

Peripheral: *Frequently involved*

- Large joints of the lower extremities (especially knees)

Dactylitis (sausage digit): Very specific for a spondyloarthropathy

Enthesitis

Hallmark feature

Inflammation at the transitional zone where collagenous structures such as tendons and ligaments insert into bone

Common sites: plantar fasciitis, Achilles tendonitis; but any enthesis can be involved

Mucosal

Oral ulcers (generally painless)

Sterile dysuria (occurs with both post-venereal and post-dysentery forms)

Cutaneous

Keratoderma blennorrhagicum: Pustular or plaque-like rash on the soles and/or palms

Grossly and histologically indistinguishable from pustular psoriasis

Can also involve nails (onycholysis, subungual keratosis, nail pits), scalp, extremities

Circinate balanitis: Erythema or plaque-like lesions on the shaft and/or glans of penis

Ocular

Conjunctivitis: Typically during acute stages only

Anterior uveitis (iritis): Often recurrent

Rarely described: Scleritis, pars planitis, iridocyclitis, and others
Cardiac
Pericarditis (uncommon)
Chronic Symptoms (>6 months)
Articular
Axial: Sacroiliac joints

- Lumbar spine
- Thoracic spine
- Cervical spine
- Cartilaginous joints (symphysis pubis; sternoclavicular joints)

Peripheral: Large joints of the lower extremities (especially knees)
Dactylitis (sausage digit): Very specific for a spondyloarthropathy
Enthesitis
Chronic inflammation can cause collagen fibers to undergo metaplasia forming fibrous bone
Chronic enthesitis leads to radiographic findings:
Plantar/Achilles spurs
Periostitis
Non-marginal syndesmophytes
Syndesmoses of the sacroiliac joints
Mucosal
Sterile dysuria
Cutaneous
Keratoderma blennorrhagicum
Circinate balanitis
Ocular
Anterior uveitis (iritis): Often recurrent
Rarely described: Scleritis, pars planitis, iridocyclitis, and others
Cardiac
Aortic regurgitation
Valvular pathologies

ReA represents an inflammatory syndrome that occurs 1–4 weeks, or possibly longer, after an infection with one of the five well-recognized etiologic triggers, namely, *C. trachomatis*, Salmonella, Shigella, Campylobacter, or Yersinia. As noted, data exist suggesting other potential triggers. When patients develop ReA, they typically present with an acute, sometimes even fulminant, inflammatory syndrome. The majority of patients will experience spontaneous resolution of their symptoms within the first 6 months, but a sizeable percent of patients can develop chronic disease, that is, disease lasting more than 6 months. The percentage of patients that develop chronic disease has been debated extensively, but much of the available data suggest that the number ranges from 10% to 30% [18]. In patients with chronic ReA, the symptoms will often wax and wane with no evidence of reinfection with an inciting organism.

It should be stressed that ReA is a very specific diagnosis; it is inherently linked to these etiologic agents. The term is often misused as a general term for arthritis that occurs secondary to other triggers, such as viruses, tick-borne vectors, etc. When the term ReA is misemployed in such fashion, it only serves to further cloud a condition of which much is already shrouded in mystery. The term ReA should only be used in its proper medical context.

Some of the earlier descriptions of ReA outlined three specific clinical features: arthritis, urethritis, and conjunctivitis. Because of these early descriptions, this has traditionally been referred to as the "classic triad of symptoms." However, we now know that the majority of patients with ReA do not present with this "classic triad" [18]. These three symptoms will be discussed first and then a more complete picture of the possible clinical features will be detailed.

The inflammatory articular symptoms often include the large joints of the lower extremities. Patients most often present with an oligoarthritis, but they can also have a polyarthritis or a monoarthritis. The most common joint thought to be involved is the knee. However, the inflammatory arthritis of ReA can involve any peripheral joint. About 50% of the patients also have arthritis in upper limbs. A mild polyarticular form of arthritis in small joints can also occur [18].

In terms of axial versus peripheral disease, the data are limited. The arthritis pattern of ReA is generally felt to be consistent with a peripheral SpA. As discussed above, large joints of the lower extremities are predominant, most often in an oligoarticular pattern. However, a review of the available literature suggests that axial disease might be under-recognized. One study that analyzed patients with ReA demonstrated that 49% had back pain as part of their initial presenting symptoms [39]. As a comparison from the same study, 28% of patients with psoriatic arthritis (PsA) had this same complaint. In this same study, 14% of patients with ReA presented with sacroiliitis compared to 7% with PsA. Another study assessing the lumbosacral radiographic findings of 95 patients with chronic ReA, demonstrated that 23% of them had grade 2–4 sacroiliitis and 14% had syndesmophytes [40] (Figs. 35.1 and 35.2). Both of these radiographic findings were significantly more common in post-venereal compared to the post-dysentery variant ReA and both indicate axial disease. It has been shown that the vast majority of patients with chronic Chlamydia-induced ReA have axial involvement, and 90% had evidence of at least grade 2 unilateral sacroiliitis [18]. It is important to note that the radiographic features of ReA, and perhaps particularly the axial radiographic findings, can take years to manifest. This might lead to under-recognition of the axial

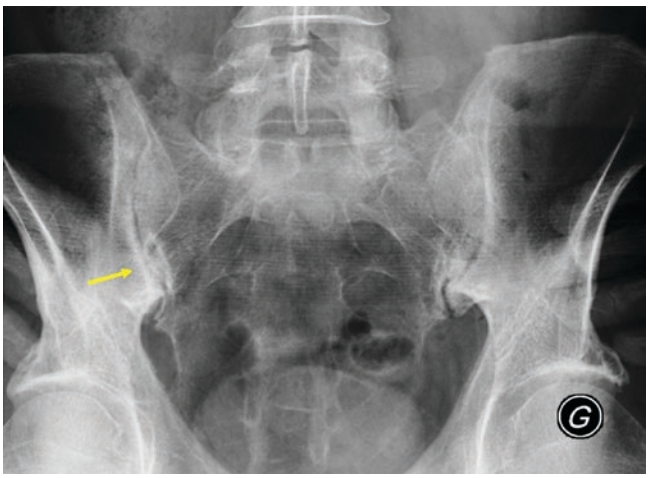

Fig. 35.1 Note narrowing and sclerosis at the inferior portion of the right sacroiliac joint *(arrow)*. Sacroiliitis in patients with reactive arthritis tends to be asymmetric and without ankylosis. (From Lukas et al. [76]. Reprinted with permission from BJM Publishing Group Ltd.)

features in patients with acute disease. Taken together, the data suggest that patients with acute ReA typically present with a peripheral oligoarthritis, but that axial features are not uncommon and that the axial features might predominate in those who develop chronic disease. Genetic features, such as HLA-B27, are likely responsible for the apparent axial predilection in chronic disease.

A couple of hallmark features of the inflammatory articular disease in patients with SpAs, in general, include enthesitis and dactylitis. Enthesitis is inflammation at the site where tendons or ligaments attach to the bones and it is very common in patients with ReA. A site of enthesis is anatomically unique in that there is little to no cortical bone interface at this site of insertion. Two different types of entheses are known in the human body, but both seem to be susceptible to inflammation in ReA [41]. Some data suggest that enthesitis is more common than synovitis in patients with ReA [21]. Common clinical forms of enthesitis in ReA include plantar fasciitis, Achilles

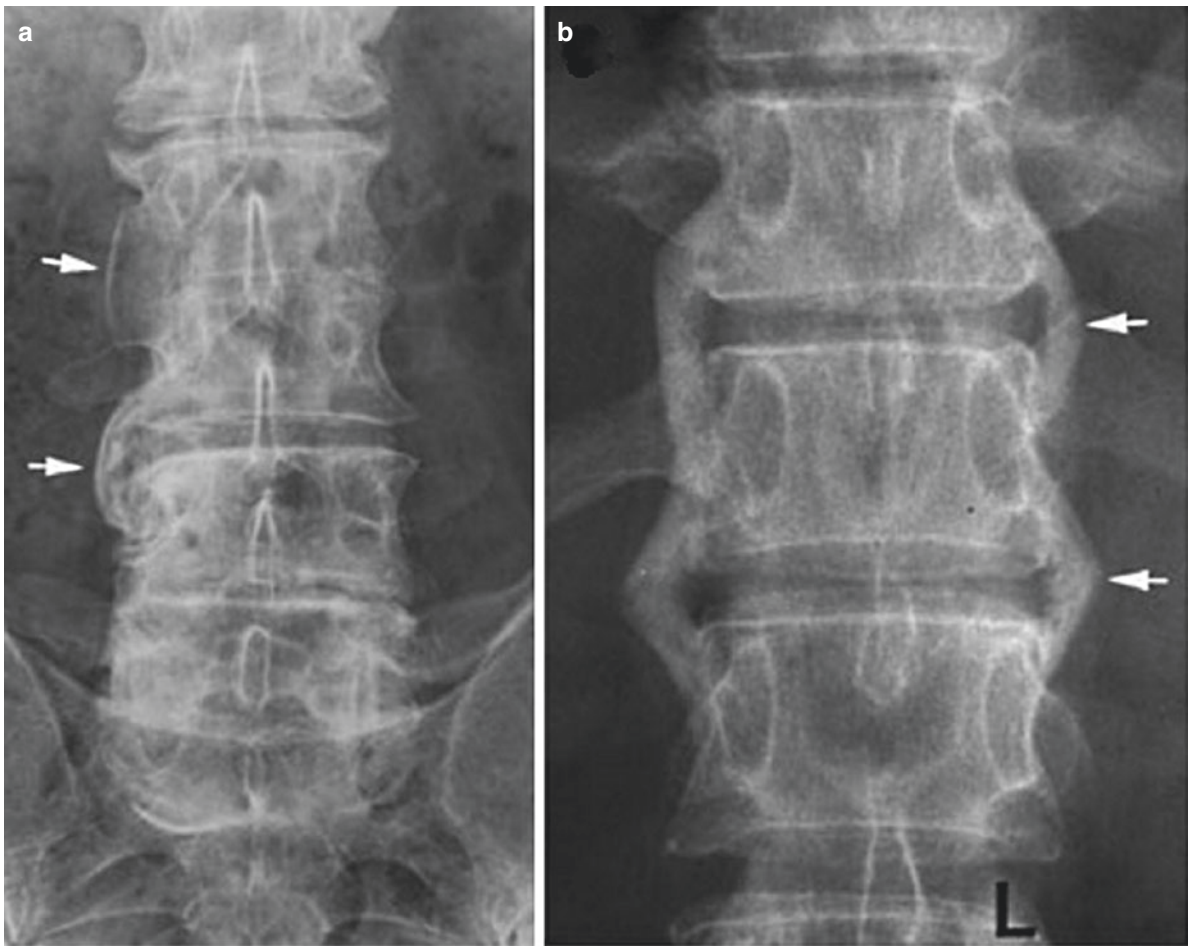

Fig. 35.2 Non-marginal syndesmophytes are thick, comma-shaped bony bridges from one vertebral body to the next adjacent one. (**a**) AP lateral radiograph of the lumbar spine in a 48-year-old man with PsA showing voluminous paravertebral new bone formation *(arrows)* in addition to fusion of the second and third vertebral bodies. There was no concomitant sacroiliitis. (**b**) AP radiograph of the thoracolumbar junction in a female patient with axial PsA demonstrating coalescing paravertebral ossifications *(arrows)*. These findings are exactly the same in reactive arthritis.(From Jurik [77]. Springer Berlin Heidelberg/ Springer Open)

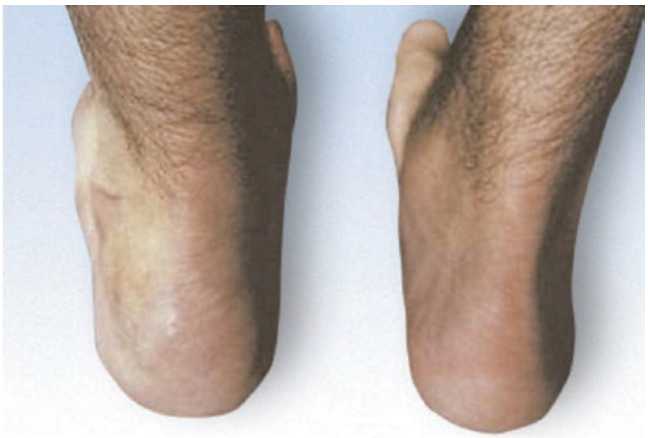

Fig. 35.3 Enthesitis. Inflammation and swelling at the insertion point of the left Achilles tendon. These findings are exactly the same in reactive arthritis. (Courtesy of Rieke Alten, Berlin. From Koehm and Behrens [78]. © Springer International Publishing Switzerland 2016)

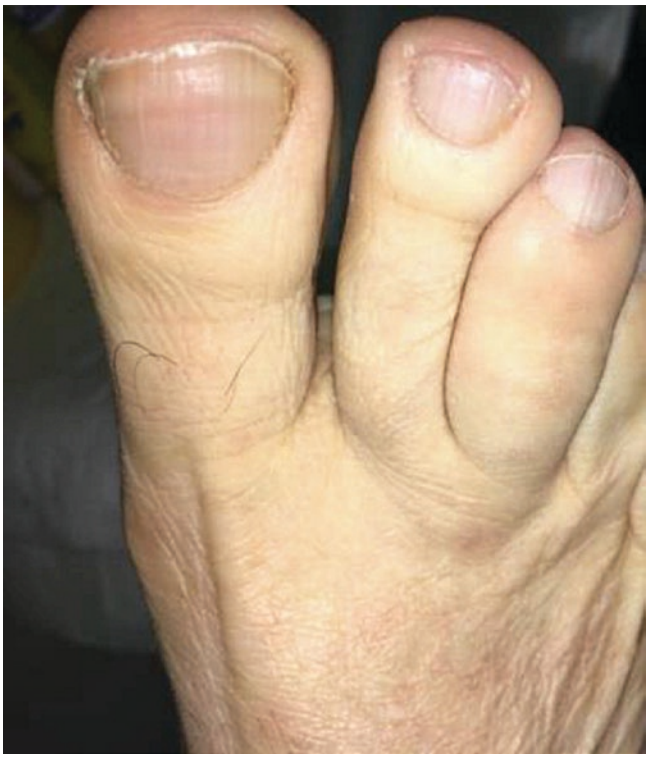

Fig. 35.4 Dactylitis. Diffuse swelling of a toe or finger as seen on the third toe in this patient. These findings are exactly the same in reactive arthritis.(From Pelechaset al.[79]. © Springer Nature Switzerland AG 2019. Reprinted with permission)

tendonitis (Fig. 35.3), and medial and lateral epicondylitis. Active enthesitis has been documented between 50 and 60% of patients with chronic CiReA, specifically [18, 42]. Dactylitis is also seen in patients with ReA, but data demonstrating the prevalence are scant (Fig. 35.4). One study suggested that it was present in 28% of patients with ReA [43]. It is generally felt that dactylitis is less common in ReA than in PsA.

Besides inflammatory articular disease, the second component of the "classic triad" of ReA includes the eye. The most common form of eye involvement in ReA is a distinguishing feature from the other types of SpA, namely, conjunctivitis. This tends to be a common phenomenon in acute ReA and occurs less frequently in chronic disease. In a Russian cohort of over 250 patients with ReA, 51% suffered from conjunctivitis [44]. When conjunctivitis occurs, it is most often bilateral. Acute anterior uveitis (iritis) can also occur in ReA patients, but it appears to be a less common problem than conjunctivitis. However, it is more commonly seen in ReA than in other types of peripheral spondyloarthritis, such as PsA. In contrast to conjunctivitis, which is seen more often in the setting of acute ReA and then typically self-remits, uveitis can also occur in the acute setting but is more often chronic and intermittent. In this same Russian cohort mentioned above, uveitis was more common in patients with chronic ReA. As is the case with chronic axial disease, HLA-B27 likely plays a role in those with chronic intermittent uveitis. The predilection for eye involvement in patients with ReA and the propensity to develop chronic involvement in the form of uveitis are intriguing given the recent findings regarding the potential role that ocular chlamydial serovars play in ReA.

Urethritis is a common clinical manifestation in patients with ReA and this feature completes the "classic triad." Urethritis and cervicitis can be seen in the post-venereal form of ReA. Interestingly, it has also been reported in the post-enteric form of ReA [18]. The urethritis is typically sterile by routine cultures; this finding mirrors that of the synovium. It should be noted that the absence of such symptoms does not rule out the diagnosis. As stated, it appears likely that, with CiReA specifically, asymptomatic initial infection can still elicit disease.

The "classic triad" of symptoms traditionally used to describe ReA has very likely led to under- and/or misdiagnosis. The majority of patients with ReA do not present with the "classic triad" of symptoms [18]. Therefore, this triad of symptoms needs to be de-emphasized. One organ system that is also frequently involved in ReA is the skin. The typical skin lesions include keratoderma blennorrhagicum, circinate balanitis, and nail changes; oral ulcers have also been reported. The oral ulcers are generally painless. Keratoderma blennorrhagicum is a pustular and/or papulosquamous rash that occurs on the palms and/or soles of the feet. Keratoderma blennorrhagicum is clinically and histologically indistinct from palmoplantar pustular psoriasis. It has been demonstrated to occur in about 20% of cases of ReA [45]. Circinate balanitis is a similar rash that occurs on the glans penis, less often on the scrotum. Estimates also suggest it occurs in ~10–15% of cases [45, 46]. Similar to

keratoderma blennorrhagicum, the histologic features of circinate balanitis are similar to pustular psoriasis [47], and chronic cases can look like plaque psoriasis. Nail changes include onycholysis and pitting and occur in about 10% of patients [45].

Finally, there are rare reports of cardiac involvement in ReA. These include cases of pericarditis, arrhythmias, aortic regurgitation, and valvular pathologies. However, rare pericarditis is more often seen in acute ReA and the other pathologies are more typical of chronic ReA.

Treatment

Clinical trial data has yet to define the single best treatment for ReA. Data exist suggesting that the most efficacious treatment might depend on the triggering organism. Unlike data with other types of SpA, most notably PsA, virtually no data exist indicating the ideal treatment for patients with axial versus peripheral disease. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, traditional disease-modifying antirheumatic drugs (DMARDs), biologics, and antibiotics have been studied as potential therapeutic agents for patients with ReA.

In patients with acute ReA, the initial treatment approach is typically conservative, that is, NSAIDs. The explanation for this initial conservative approach is twofold. First, as stated, a large percentage of ReA cases are self-limiting, so this conventional approach is often warranted. Second, because of the many factors listed earlier in this chapter, ReA is often underdiagnosed so more focused therapies might not be considered. Clinical experience tells us that NSAIDs are effective as a treatment for ReA, but there are only two small prospective trials that have formally evaluated their use. The first was a study comparing azapropazone (available in the UK) to indomethacin in patients with both psoriatic arthritis and ReA [48]. This study, which only included 16 patients with ReA, suggested that indomethacin might be more effective than azapropazone in treating the articular manifestations of ReA. However, there were more side effects with indomethacin. The second study compared ketoprofen to indomethacin [16]. In this study of 50 subjects with ReA, both ketoprofen and indomethacin were equally efficacious at treating the articular symptoms of ReA. As with the other study, there were more side effects with indomethacin. Both studies primarily assessed the effect on peripheral arthritis.

The acute symptoms of ReA can range from mild to fulminant. Oral corticosteroids are often used in those who do not respond to NSAIDs. Some data indicate that corticosteroids might have limited benefit for the axial symptoms and may be more effective for the peripheral arthritis of ReA [49]. Because the knee is commonly affected in acute ReA, intra-articular steroids can be quite effective in the setting of acute ReA. Topical corticosteroids are the initial treatment for many of the extra-articular features of ReA, including iritis/uveitis, keratoderma blenorrhagicum, and circinate balanitis [49]. In patients with HIV infection and ReA, many of whom have skin lesions, the lesions respond well to antiretroviral therapy [16]. However, an avenue of research yet to be explored includes the potential long-term sequelae of using corticosteroids, particularly oral and/or intra-articular, in acute disease. Because certain bacteria are the defined etiologic agents of ReA and these same viable bacteria or bacterial fragments have been identified in the synovium, the possibility exists that such treatment might predispose to chronic ReA. This is an area requiring further research.

A final point regarding treatment of acute ReA relates to prompt treatment of the initial inciting infection. As might be expected, prompt treatment of the triggering infections with antibiotics decreases the likelihood of development of post-venereal ReA [50]. Specifically, antibiotics that are active against *C. trachomatis* are more effective at preventing post-venereal arthritis than those that are not. Along those same lines, it would seem logical that the initial treatment of the gastrointestinal infection with antibiotics would decrease the chance of developing post-dysentery ReA. However, the fact remains that even with the treatment of the initial infection with antibiotics, whether it is venereal or gastrointestinal, this does not preclude the development of ReA. To complicate matters, data demonstrate that in the case of *C. trachomatis*, asymptomatic initial infections can still incite ReA [18, 42]. It is possible that subclinical infections or inoculations with the gastrointestinal causative organisms might do the same.

As stated, ReA has the capability of progressing to chronic disease. It also can cause joint damage if left untreated, especially in patients with chronic ReA. The potential radiographic damage can mirror those of other types of SpA, especially psoriatic arthritis. These radiographic sequelae can include both the axial and peripheral skeletal system. For these reasons, traditional DMARDs are often utilized in patients with ReA.

The most rigorously studied DMARD in the setting of ReA is sulfasalazine (SSZ). The efficacy of SSZ in ReA has been analyzed in two prospective, double-blind studies. The first trial assessed SSZ (2000 mg/day) in 134 subjects with chronic ReA with a mean disease duration of approximately 10 years [51]. Eligible subjects had failed NSAIDs and were followed for 36 weeks. The results were mixed, but both the axial and peripheral manifestations were assessed. The overall response rates, which were determined by peripheral arthritis scores and physician global assessment, were 62.3% in the SSZ group and 47.7% in the placebo group ($P = 0.089$). A measurement of axial improvement, the Spondylitis Articular index, barely achieved significant improvement with a p value of 0.05. A longitudinal analysis also revealed significant improvement in the subjects taking SSZ compared

to placebo ($P = 0.02$). Although the inclusion criteria required several features consistent with ReA, there was no effort to determine if subjects with post-enteric ReA might have fared better than those with the post-venereal type. SSZ was analyzed in another study of 6 months duration and 79 participants [52]. A slightly higher dose of 2–3 grams/day was analyzed. An important difference with this trial was that it included participants with acute disease; their mean disease duration was approximately 4 months. There was no significant difference between the two groups in terms of pain, number of swollen joints, and Erythrocyte Sedimentation Rate (ESR). Because acute ReA often remits spontaneously, significant improvement was noted in both the SSZ and placebo-treated patients. There was no difference in efficacy regarding the initial triggering infection, HLA-B27 status, or presence of axial arthritis. The primary adverse events in subjects on SSZ in both studies were gastrointestinal in nature.

The most commonly employed traditional DMARD across all types of inflammatory arthritis, including the SpAs, is methotrexate (MTX). Indeed, MTX is likely the most frequently used traditional DMARD in patients with chronic ReA. In spite of this rather frequent use, there are no clinical trials that have assessed the potential efficacy of MTX in ReA. As stated, out of all the types of SpA, PsA most closely resembles ReA. Recent data has questioned the efficacy of MTX in PsA [53]. This study primarily assessed the efficacy of MTX on the peripheral symptoms of PsA. These data might cause concern about a similar lack of efficacy in ReA. Several trials have assessed the response of the axial symptoms to MTX in other types of SpA and these studies have suggested no benefit [54]. Taken together in this era of evidence-based medicine, it is hard to justify the use of MTX in ReA. Future studies are needed in this regard. There are also no studies with hydroxychloroquine, leflunomide, azathioprine, or cyclosporine in ReA.

The first group of biologics available to patients was the tumor necrosis factor-alpha inhibitors (TNFi). The TNFis have been studied extensively in SpA and have revolutionized the treatment of most types of SpA including PsA and AS. Therefore, it would be logical to expect a similar response in ReA. However, the data regarding the use of TNFi in the setting of ReA are still rather scant. Regarding the pathophysiology of ReA, studies have demonstrated that ReA patients have higher serum TNF-alpha than normal controls, but lower levels compared to other types of inflammatory arthritis [55]. Other studies suggest ReA is more of a Th2-driven disease [56, 57], but this might depend on the types of cells analyzed. With Chlamydia-induced ReA, there might be specific concerns regarding the use of TNFi. The synovial-based chlamydial organisms remain viable and in vitro data has demonstrated that persistent chlamydial levels are inversely proportional to TNF-alpha levels [58–60].

Several case reports and two small open-label studies suggest clinical benefit with TNFi in the treatment of ReA [61–64]. The first open-label study assessed etanercept in 16 patients with undifferentiated or reactive arthritis [63]. Ten of the sixteen patients completed the 6-month study. Nine of the ten completers were considered responders; however, one of these patients required a total knee replacement 6 months after beginning the therapy. In the second open-label study, 9/10 patients demonstrated a response to treatment with their TNFi; however, it should be noted that most of these patients had acute ReA at the onset of therapy, so natural disease course could have explained some of the response. Regarding other potential biologics in the treatment of ReA, there is a case report with tocilizumab, a drug that inhibits interleukin-6 [65]. The limited clinical data that we have regarding the biologics, and TNFi specifically, in ReA suggest possible therapeutic effect without evident reactivation of the inciting infection.

Because of the irrefutable fact that the genesis of ReA is an acute bacterial infection, antibiotics have been well studied as a potential treatment for ReA. Some of the more recent findings regarding bacterial persistence have further stimulated research in this regard. Indeed, antibiotics are the most extensively studied therapeutic approach for ReA. However, these studies have produced apparent conflicting results and elicit much debate. Further, the hesitancy to administer long-term antibiotics because of the fear of creating bacterial resistance serves to dissuade practitioners from this approach. Conversely, since specific bacteria can elicit disease and some of these same bacteria have demonstrated long-term viability in the end organ, that is, synovium, then this therapeutic approach could serve as a cure. What do the data show?

The earliest trial assessing the role of antibiotics in ReA analyzed 3 months of treatment with lymecycline in patients with acute ReA [66]. The findings were very interesting. There was no benefit to patients with post-dysentery ReA, but there was significant improvement in patients with Chlamydia-induced ReA. Critics have argued that the benefit might have been from the anti-inflammatory properties of lymecycline [67]; however, if this were the true effect, then both groups should have fared equally well. This led to several other studies assessing the use of various long-term antibiotics, including ciprofloxacin, azithromycin, and doxycycline. All of them provided negative results [68–72]. However, a rather salient feature of the initial study was lost in these follow-up studies; there was little effort to separate post-chlamydial and post-enteric patients in these studies. In addition, most of these studies included both acute and chronic patients. Previous studies, specifically with SSZ, had demonstrated the flaw in studying acute ReA patients. More recent reports have indicated that a prolonged course of combination antibiotics (doxycycline with rifampin or azithromycin with rifampin) represents an effective treatment specifically for chronic post-chlamydial ReA [73, 74]. This study suggested that this treatment approach can not only statistically improve the symptoms but also clear the synovial-based chlamydial infec-

tion. Recent mouse model data appear to complement these clinical trial findings. In this mouse model of Chlamydia-induced ReA, the arthritis can be prevented with combination antibiotics that were commenced on day-1 postinoculation with *C. trachomatis* [75].

Conclusion

ReA has been described for hundreds, perhaps thousands, of years. It represents the classic interplay between host and environment. Traditionally, factors affecting disease predilection have focused on the host, but the environment, that is, specific features of the triggering bacteria, might also be responsible for predicting disease. ReA is a part of the SpA family. It is traditionally felt to represent a peripheral SpA, but the existing data suggest the axial symptoms might be underappreciated. There is no question that specific bacteria can elicit this disease; indeed, the term ReA should only be used in this context. The role that these same bacteria might play in disease propagation or maintenance is less clear. Even more elusive is the role that asymptomatic initial infections might play. Because of these complexities, the optimal treatment is yet to be defined.

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Psoriatic Arthritis and Infection

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Frank Barnett Vasey and Luis R. Espinoza

Introduction

The pathogenesis of psoriatic arthritis (PsA), as in most inflammatory rheumatic conditions, represents a complex interplay of genetics and environment. This chapter will emphasize the increasing evidence that PsA is indeed a "reactive" arthritis to Gram-positive bacteria.

Lending support is a comprehensive, wide-ranging review from Icelandic authors [1]. They and their countrymen have been in the forefront of a study of tonsillar streptococci and their link to PsA and psoriasis (Ps). Information from studies of Ps is clearly relevant to understanding PsA. Only about 15% of PsA patients actually develop the joint disease before the skin disease. Genetic studies have examined the similarities and differences between the skin and joint disease.

Genetics

Understanding of the genetics of PsA has steadily progressed in recent years. The Th-17 pathway has become recognized as an important and consistent genetic influence on the pathogenesis of PsA [2]. Its location is within the major histocompatibility complex at 6p21.3. It accounts for about one-third of the genetic influence in PsA and has led to exciting new immunosuppressive therapeutic approaches for both the skin and joint disease.

Other recently recognized influences include IL-12B, IL-23R, TNIP1, TRAF31P2, FBXL 19, and RET. Genome-wide association analysis has combined several large studies by meta-analysis to improve genome-wide significance [3]. Ten regions related to PsA were detected. The PsA-specific regions were distinct from IL-23R and TNFAIP3. These studies show susceptibility variants in the IL12B, NOS2, and IFIH1 regions. Taken as a whole they reveal similarities and differences in the increasingly complex genetics of Ps and PsA. These differences may account for both the roughly 15% of patients who develop PsA before Ps and those who never get the skin disease, making the correct diagnosis next to impossible.

In most patients the psoriatic process begins in the skin. This review will also express the proviso that increasingly in all the spondyloarthropathies the bowel bacteria immune interaction is increasingly being scrutinized.

Immunology

Skin contains many epidermal and immune elements which have been termed skin-associated lymphoid tissue (SALT) [4]. T lymphocytes and macrophage lineage dendritic cells are proposed as principle mediators of disease activity. Dendritic cells release interleukin (IL)-12 and IL-23 which in turn activate IL-17-producing T cells. These cells and others stimulate psoriatic-inducing cytokines interferon gamma, tumor necrosis factor-alpha (TNF-alpha), and IL-22. Thus, components of both innate and adaptive immunity are problematic in the skin and joint disease. Epidermal keratinocytes are normal players in skin innate immunity. They have the potential to manipulate T cells to induce skin inflammation and hyperkeratosis.

A key element is disruption and amplification of the normal epidermal proliferation cycle. The basal layer graduates outward and matures normally into granular keratinocytes. These mature keratinocytes are immunocompetent and secrete antimicrobial peptides. They eventually further mature into corneocytes that form a mechanical barrier to protect the skin. Further activated keratinocytes affect multiple T helper cells (Th1, Th2, Th17, Th22) as well as macrophage lineage dendritic cells and neutrophils. Multiple chemokines mediate the activation.

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_36

Langerhans cells are immature antigen-presenting cells [5]. When activated they are mobile and represent one effector cell for PsA. Histologically, they are normally found scattered in the lower epidermis. In the skin disease they migrate to the outer epidermis and become more prevalent in the dermis as well. They express immunogenetic DR, tumor necrosis factor-alpha, and toll-like receptors among others.

Co-conspirators with the macrophage lineage cells are cells of lymphocyte origins. Multiple modern treatments that attack T cells in several ways have demonstrated benefit and became FDA approved. These include Abatacept, Alefacept, Efalizumab, Ustekinumab, and Secukinumab among others. Studies of the effects of these agents have solidified the concept that Ps is mediated by activated T cells.

Histologically, it has been shown that T cells are increased in psoriatic skin lesions. T-cell activation derives from dendritic cells. This activation is mediated by IL-23. Activated T cells produce IL-17. Additionally, there are TH1 cells producing interferon gamma and tumor necrosis factor-alpha. CD4+ and CD8+ T cells producing IL-17 have also been recognized in psoriatic skin.

In addition to the diverse evidence of immune activation, comorbidities have been recognized. These include cardiovascular disease with acute myocardial infarction, diabetes, metabolic syndrome, hyperlipidemia, and hypertension.

A number of initiating events have been recognized in the skin disease. Drugs including lithium, antimalarials, Inderal, quinidine, and indomethacin can induce psoriasis. The author believes most relevant to joints and skin are trauma known as the Koebner phenomenon and infection, most notably Group A streptococcal tonsillitis and guttate or drop-like form of psoriasis.

Inflammatory mediators diffusing from psoriatic skin could play a role as well in PsA [6]. These mediators include IL-16, IL-17, IL-18, IL-Ira, and TNF-alpha. Several chemokines CCL-5, CCL-2, and CCL-4 are also elevated in peripheral blood. They could potentially play a role in either the comorbidities or the arthritis.

The ready availability of psoriatic skin has rewarded dermatologists and patients. There is much new information on the complexity of the immune pathogenesis of the disease. The greater difficulty of obtaining psoriatic arthritis synovium and joint fluid as well as the much smaller population affected has put rheumatologists behind in understanding PsA.

Still progress has been made. In the 1970s, studies of the immune basis of PsA began in earnest. It was then generally accepted that PsA was a clinically unique entity and not the coincidental occurrence of an unrelated form of arthritis.

Early studies of humoral immunity showed evidence that immune complexes and complement components were elevated supporting the immune underpinnings of the clinical findings [7]. In the 1990s, interest in cellular immunity increased. T cells became a focus in both the skin and joints. CD8+ cells and Th17 became a focus in synovial fluid [8]. Transplantation of unaffected skin from Ps patients to SCID (immunosuppressed) mice suggested the importance of CD4+ and T cells. When they were activated and injected into the mice, a psoriatic plaque developed. CD8+ cells had no effect [9].

Although obviously less accessible than psoriatic skin, psoriatic arthritic synovium and synovial fluid have come under recent study. In synovium lining layer thickness, vascularity infiltrates of lymphocytes, plasma cells and neutrophils have been studied. Compared to rheumatoid arthritis (RA) vascularity, neutrophil and CD163 macrophage counts were increased in PsA [10]. The same authors found close similarities in findings between pauci- and polyarticular PsA. Lining layer hypertrophy was more evident in RA patients. These observations confirm pioneering work by the editor on psoriatic synovial vascularity. He showed endothelial swelling and thickening of vessel walls [11].

Psoriatic synovium and synovial fluid have come under recent study. Traditionally, the synovial fluid cell counts are typically elevated from the range of normal and that of several thousand cells per cubic centimeter (cc) seen in osteoarthritis (OA). That said, the cell counts are typically less than in rheumatoid arthritis where 20,000 cells per cc and above are more typical.

The recognition of the importance of Th17 cells in both the skin disease and the arthritis has led to genetic, cellular cytokine, and signaling molecule studies. Scarpa's Italian group studied T cell transcription, cells, and cytokines in joint fluid [12]. They were able to identify IL-23, FoxP3, JAK1 and STAT-1, STAT-3, and STAT-5 in T-cell lysates from PsA synovial fluids. They were all higher than in peripheral blood from healthy controls IL-2, IL-21 IFN-gamma was not detectable. IL-6- and IL-1-beta levels were higher in PsA patients than in synovial fluids from osteoarthritis patients. They concluded that there was a distinctive JAK1/STAT-3, STAT-5 transcriptional network on synovial fluid T cells from PsA patients. They suggested an interplay of Th17 and Treg cells with IL-6, IL-23, and IL-1-beta in perpetuating joint inflammation in PsA.

Gladman's group in Toronto focused on gene expression in joint fluid from PsA patients [13]. She had synovial fluid from 14 PsA and 9 osteoarthritis patients. This study confirmed the finding of high levels of signaling molecules STAT-3 and FoxP3 in synovial fluid cells. Their data appears discordant from the prior study in that IL-6 was more prominent in osteoarthritis synovial fluid than PsA. They concluded that there were expression differences in Th17 signaling genes comparing PsA and OA synovial fluid cells. A subset of genes was concordant in joint fluid and peripheral blood in PsA and could be a biomarker.

Much work in innate acquired immunity in parallel with that on the cutaneous disease has been conducted on PsA patients. As in Ps, the Th17/IL-23 axis has been identified as

playing an important role. In PsA, the inciting event is activation of antigen-presenting cells. In the last portion of this chapter, the thesis that Gram-positive bacteria are the missing link antigen will be presented. T cells in circulation, skin, and synovium are activated.

In the arthritis, as in the skin, blocking downstream Tumor Necrosis Factor has been very effective for many but not for all PsA patients. Clearly a level of understanding is missing. Osteoclasts and neutrophils have attracted attention. RANK and RANK L are expressed by bone-forming osteoblasts under physiological conditions. RANK L is secreted as a soluble protein. It interacts with RANK a transmembrane receptor on osteoclasts and dendritic cells to produce multinucleated osteoclasts that resorb bone.

A role for this mechanism in the enthesopathy of PsA would be attractive. The inflammation where tendon attaches to bone is a hallmark of PsA not typically seen in RA. Rank is expressed in psoriatic synovium. Both IL-17 and IL-23 upregulate its expression.

The lack of response to TNF blockade in some patients suggests other factors play an important role. One of these could be the NF-Kappa B transcription family. Activity of these pathways has been confirmed in PsA [14]. TNF blockade did not affect this pathway. Studies of genome-wide association scans have found susceptibility genes associated with NF-Kappa B in PsA [15]. Another locus identified by GWAs is an interacting protein Act 1. This could contribute to skin and joint inflammation as well as bone destruction [16].

Ritchlin et al. have studied osteoclast activity and bone remodeling in PsA. High-resolution imaging shows that new bone formation is focused on entheseal sites [17]. These observations support the clinical observation that mechanical stress and trauma focus the immune attack in PsA. IL-23/IL-17 pathway plays an important role in this bone remodeling and potential destruction.

Neutrophils have received little attention to date in PsA. They do form Monroe micro abscesses in the skin, and they are the predominant cell in PsA synovial fluid. In most cases, they are not particularly dense in synovium. Still IL-23/IL-17 activation by NF-Kappa B produces granulocyte-colony- and granulocyte-macrophage-stimulating factors and various chemokines. A better characterized subset of neutrophils could well play an important role in TNF blockade refractory PsA.

Psoriatic Monocyte/Macrophages

The authors have always thought that macrophage lineage cells activated by Gram-positive bacteria are the "smoking gun" in the pathogenesis of PsA. Additionally, a bacterial-processing defect allowing prolonged activation is required.

Macrophages are an integral part of the innate or hereditary immune defense system against pathogens. Fortunately, they are coming under study in PsA. They have been divided into M1 and M2 [18]. The former release high levels of inflammatory cytokines with nitrogen and oxygen radicals killing microorganisms. M2 conversely resolves inflammation by phagocytosis of apoptotic cells and release of mediators of tissue remodeling angiogenesis and wound repair.

The total number of macrophages in synovium is similar in RA and PsA. Interestingly, the M2 subset was clearly over expressed by CD163. This was similarly seen in synovial fluid [18]. The predominance of these cells could be responsible for the pro fibrotic state and syndesmophyte formation through abnormal tissue remodeling.

A Dutch group has approached bacterial handling by macrophage lineage cells described as dendritic cells derived from peripheral blood mononuclear cells [19]. They studied CD163 M2 cells. They noted that they are frequent in psoriatic synovium. They found that CCRS was increased. This is a chemokine receptor on the surface of white cells.

Toll receptors 2 and 4 with CD14 were comparable to normals. When these cells were incubated with Gram-negative heat-killed *Escherichia coli* and *E. coli* lipopolysaccharide, IL-6 was markedly elevated. TNF-alpha and IL-10 were not. These cells were less successful in suppressing cytokines from dendritic cells than normal M2 cells. They concluded that M2 cells from PsA have a clearly aberrant phenotype and could fail to suppress ongoing joint inflammation in PsA [19]. It would have been interesting to see the effect of Gram-positive cell walls and peptidoglycan in their experimental model.

Infection

There has accumulated for many years evidence that Gram-positive bacteria play an important role in the pathogenesis of Ps and PsA. The concept that PsA and RA were distinct disorders was gaining traction in the 1950s.

The first large scale study in 1952 was done in Scandinavia by Norholm-Pederson who studied 133 Ps patients [20]. Forty-four percent had intermittent streptococcal infections usually tonsillitis and 21% had a positive throat culture. He noted the association with guttate Ps, but also overlap with plaque Ps. There was no note of PsA.

Tervaert et al. divided 200 Ps patients into three groups: acute guttate, chronic plaque, and acute plaque. Throat cultures for Group A streptococci were positive in 82%, 71%, and 34%, respectively [21]. Group B streptococci were found in 0%, 19%, and 33%, respectively. No notations on the presence of PsA were made. The authors wondered if the dermal vascular changes could be a direct or indirect effect of the bacterium.

The authors' interest in the question was stimulated by Quimby [22]. They determined serum titers of antibodies to deoxyribonuclease-B in 71 Ps patients. This is a streptococcal exotoxin. They found 41% of those with Ps were positive. They did note who had inflammatory arthritis and 10 of the 17 (51%) were positive.

The authors' similar ELISA determination focusing on 49 PsA patients had identical 51% positive patients with 10–20% positivity in normals and RA controls [23]. This was statistically different.

Experimentally, Wilder [24] and Schwab [25] have shown in genetically susceptible rat strains that peptidoglycan-polysaccharide fragments from Group A streptococci can induce a chronic erosive arthritis.

Two studies focusing on Gram-positive bacteria have been supportive. The authors [26] looked at V2 regions of 16S ribosomal RNA from Group A and B streptococci in peripheral blood from PsA patients. Reverse transcription-polymerase chain reaction was utilized in 19 PsA patients. Seven were positive for Group A streptococci and two for Group B. Seventeen RA patients were uniformly negative.

A similar study from the UK in Ps patients had similar results and provided a possible explanation for PsA and Ps patients that lack humoral or cellular evidence of streptococcal immune activation [27]. Eight of twenty Ps patients have ribosomal DNA evidence of streptococci. Most had guttate Ps. Most of the others with plaque had evidence of staphylococci in peripheral blood. Thus 17 out of 20 had strep or staph or both in their blood. All controls were negative in both studies.

The editor in early work showed that toll receptor 2 is upregulated in psoriatic arthritis [28]. This highly conserved cell surface protein is widely found in human immunocompetent cells. While not specific for Gram-positive bacteria, lipoteichoic acid in the cell wall of these bacteria is a major agonist.

The finding of elevated serum IgA in PsA heralded the important recent study of the heavy gut microbial load known as the microbiome [29].

A recent review from Iceland has addressed infections and the risk of PsA in a comprehensive fashion [1]. They noted environmental factors including stressful life events, trauma, climate, diet, and smoking, but stressed infection. They reviewed 4747 articles. They deleted case reports of five or fewer cases. They reviewed in detail 27 studies. These included 933 PsA patients and 1611 controls. While there was some inconsistency, four of six studies of streptococci were positive. Two studies of staphylococcal super antigens were positive which supports Baker's previously discussed work in Ps patients. These observations taken as a group argue that Gram-positive bacteria play a cardinal role in the pathogenesis of PsA in most patients.

That does not rule out a role for other infectious agents including human immunodeficiency virus (HIV), forms of chlamydia or Gram-negative organisms in certain patients. The editor described a young man with HIV and severe destructive PsA whose rapid progression was exceptional [30].

The most detailed study of this association has come from Zambia [31]. Authors noted PsA was 25 times higher in their population than in a European population. And this had occurred in a Zambian population in whom PsA was rare.

The microbiota has also been shown to play a potential role in both psoriasis and PsA [32–34]. Microscopic gut inflammation is observed in most patients with PsA, and about 40–50% of them exhibit macroscopic inflammation in the absence of overt bowel symptomatology [35]. These gut inflammatory changes may lead to changes in the gut microbiota composition, dysbiosis, and as a result the potential development of inflammatory musculoskeletal involvement. The gut mucosa is populated by a variety of effector and regulatory T and B cells, as well as some specialized innate-like T cells, which are predominantly found at mucosal and epithelial barrier sites, where they serve a key role in modulating host-microbial interplay. The gut microbiota of PsA and patients with psoriasis has been shown to exhibit reduced bacterial diversity when compared to that in healthy controls, findings that are very similar to that seen in patients with inflammatory bowel disease [32–34]. Both PsA and psoriasis patients showed a relative decrease in abundance of Coprococcus species, while gut microbiota from PsA patients was also characterized by a significant reduction in Akkermansia, Ruminococcus, and Pseudobutyrivibrio [34]. These findings support the notion that dysbiosis in the gut microbiota is intrinsically related to the inflammatory changes observed in both the skin and joints in psoriasis patients, and it deserves further investigation. Its potential therapeutic value also deserves further investigation.

Evidence of a critical role for infection in PsA has never been stronger. Infection may be an inappropriate term in the sense that the usual cardinal features of "calor, dolor, rubor" are missing yet immune activation and attack on skin and joints are occurring. Group A streptococci remain uniformly sensitive to penicillin. Could a rheumatic fever prophylaxis approach with intermittent use be helpful in streptococci sensitive patients? Culturing peripheral blood mononuclear cells from Ps and PsA patients and exposing them to Gram-positive bacteria would be of interest. There must be a killing defect and/or a cell wall digestion problem resulting in prolonged immune activation.

Despite the progress on this fascinating skin and joint condition, challenges to future investigations remain.

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Microbes in the Pathogenesis of Inflammatory Bowel Disease: A Review

37

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Introduction and Background

It has been well said that the human body is nothing but a vessel to carry microbes. One of the places the microbes are abundant and contribute in a number of ways is the gastrointestinal system. The host–microbe interactions in the gastrointestinal tract are bidirectional, complex, and not well understood. These host–microbe interactions in the gastrointestinal (GI) tract and especially the intestines and colon can be mutually beneficial or have adverse effects that contribute to inflammation.

On the one hand, intestinal microbial colonization is essential to nutrition, energy metabolism, and proper "conditioning" of the gastrointestinal and peripheral immune systems. On the other hand, the GI lumen can contain microbiota and microbial-derived factors that may promote inflammatory bowel disease (IBD) in the context of an underlying genetic immune defect.

The intestinal microbiota is acquired at birth but changes rapidly during the first year of life; thereafter there are only minor changes throughout childhood. In adults, each person's unique population of fecal microbiota is fairly stable over time, but fluctuations occur in response to environmental and developmental factors and in disease.

Intestinal microbiota and the ability of the host to recognize and respond to this microbiota are important in the generation and optimal function of intestinal antimicrobial proteins, epithelial cells, immune cells, cytokines, and immunoglobulin A (IgA). The host immune system, various host conditions (obesity) and environmental factors (diet, antibiotic exposure) can influence intestinal microbial communities. The microbial community alterations can, in turn, modulate intestinal inflammatory outcomes. In patients with IBD, alterations in both the diversity and density of bacteria, in specific bacteria directly associated with the mucosa, and in the functions of the bacteria present (oxidative stress) have been described, further suggesting a significant role of intestinal microbiota in the pathogenesis of IBD.

This chapter strives to shed light on the current understanding of this complex interaction and how it contributes to the pathogenesis of inflammatory bowel disease.

Epidemiology

In North America, incidence rates of IBD range from 2.2 to 19.2 cases per 100,000 person-years for ulcerative colitis (UC) and 3.1 to 20.2 cases per 100,000 person-years for Crohn's disease (CD) [1, 2]. Microbes play a significant role in its development as suggested by the correlation between specific microorganisms and IBD and the association between acute gastroenteritis and IBD. A case control study suggested that the risk of IBD was significantly increased in patients with a prior episode of acute gastroenteritis (OR 1.4; 95% CI 1.2–1.7) [3]. A separate population-based cohort study of patients with documented Salmonella or Campylobacter gastroenteritis also showed an increased risk of IBD, when compared with a matched control group (1.2% vs. 0.5%, HR 2.9, 95% CI 2.2–3.9) with the highest risk being in the first year after the gastroenteritis episode [4].

Pathogenesis of IBD (Fig. 37.1)

Inflammatory bowel disease (IBD) is an immune-mediated chronic intestinal condition. It represents heterogeneous disorders affecting the gastrointestinal tract. Two major types

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_37

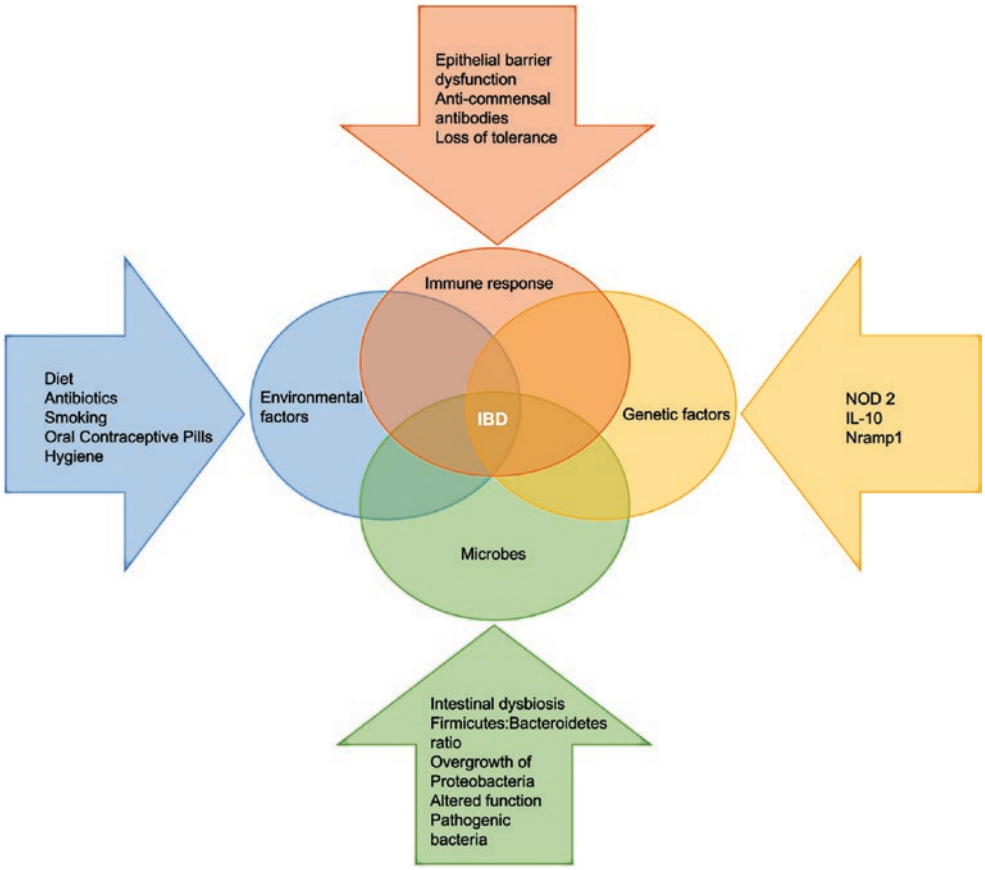

Fig. 37.1 Pathogenesis of IBD: a multifactorial concept

of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Ulcerative colitis is a chronic inflammatory disease limited to the mucosal layer of the colon. It nearly always involves the rectum and usually extends in a proximal and continuous fashion to involve other portions of the colon. Crohn's disease is a chronic inflammatory disease characterized by transmural inflammation and by skip lesions. Accumulating evidence suggests that inflammatory bowel disease results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host [5].

The human gastrointestinal tract harbors a hundred trillion different microbial organisms, including bacteria, viruses, fungi, and protozoa; this constitutes the microbiota also referred to as microbial flora [6]. Resident bacteria outnumber human somatic and germ cells tenfold and represent a combined microbial genome well in excess of the human genome and thus microbiota has the metabolic activity of a virtual organ within an organ [7]. A healthy gut microbial flora is very important for gastrointestinal functions like development of the immune system, development of host defenses, and supply of nutrients and energy. The fetal gastrointestinal tract is sterile, and colonization begins immediately after birth, which is influenced by diet, medications, and hygiene levels [7]. The establishment of a stable gut microbiota generally accompanies two big transitions in infancy. The first transition occurs soon after birth, during lactation, and results in dominance of the gut microbiota by Bifidobacterium. The second transition occurs during the weaning period, with the introduction of solid foods and continuation of breast milk feeding, and results in the establishment of an adult-type complex microbiome dominated by the phyla Bacteroidetes and Firmicutes [8].

At present, the exact etiology of IBD is unclear. However, it is believed that disruption of the immune system and/or imbalanced interactions with microbiota leads to the development of chronic intestinal inflammation and the potential addition of environmental factors triggers genetically susceptible hosts [9]. In the following section, we will be talking briefly about the different known etiologies/pathogenesis for IBD at this time.

Environmental and Genetic Factors

Important environmental risk factors for the pathogenesis of IBD include smoking, diet, antibiotics, and oral contraceptives pills (OCPs) [10, 11]. Multiple theories have been proposed to explain the unknown environmental exposures that may interact with the immune system and result in an abnormal inflammatory response to intestinal microflora. The most

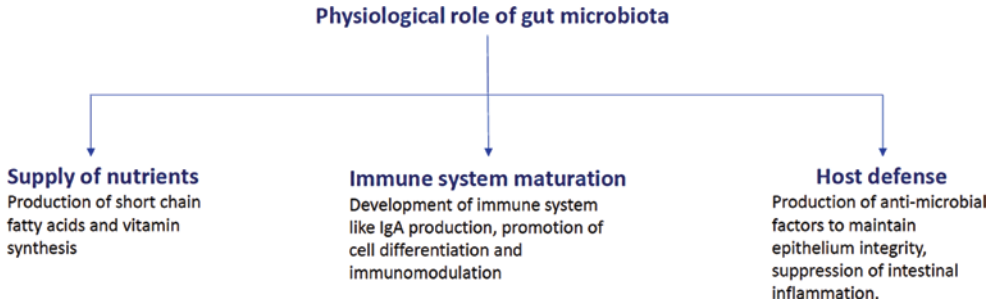

Fig. 37.2 Physiological role of gut microbiota

predominant theory is the hygiene hypothesis. This hypothesis proposes that the rising frequency of immunologic disorders can be attributed to a lack of childhood exposure to enteric pathogens. Improved sanitation and hygiene, along with decreased exposure to enteric organisms during early childhood, may lead to a greater susceptibility to develop an inappropriate immunologic response upon exposure to new antigens (e.g., a gastrointestinal infection) later in life [10].

Since the discovery of nucleotide-binding oligomerization domain-containing 2 (NOD2), more than 160 IBD-associated gene loci have been identified. NOD2's involvement in microbial sensing, innate and adaptive immune activation, plus its role in autophagy, the gut epithelial barrier, and shaping the gut microbiota suggest that it is a versatile protein with many roles in IBD pathogenesis. These genetic associations highlight the importance of gene–microbe–environment interactions in IBD pathogenesis. Smoking is a major environmental risk factor, with evidence for gene–microbe interactions in its contribution to disease. It has been independently demonstrated that NOD2 −/− mice have altered gut microbiota composition, and that cigarette smoke can alter NOD2 expression and function in intestinal epithelial cells [11].

Similarly, diet is another environmental risk factor for the development of inflammatory bowel disease. Studies have shown how dietary habits result in compositional changes to the microbiota and could theoretically lead to inflammation in genetically susceptible individuals. A report has shown increased dietary intake of n-6 polyunsaturated fatty acids and animal protein together with a change toward a more westernized diet increases the risk of IBD. On the other hand, surveys and case control studies have shown that a range of other dietary factors, such as refined sugar, fast foods, margarine, and dairy products increase the risk of IBD, while vegetables, fruits, fish, and dietary fiber appear to have a protective effect [11, 12].

Gut Microbiota in IBD

The gut microbiota forms a natural defense barrier and provides numerous protective, structural, and metabolic effects to the host [7, 8] (Fig. 37.2). Commensal microbes are source for nutrients and energy, like production of short-chain fatty acids (SCFAs) and vitamin synthesis. They also help in the development of immune systems like IgA production and regulation of T-helper cell. Last but not least, microbiota is also involved in the host defense, like in the production of bacteriocins and lactic acid, which act as antimicrobial factors [7, 8].

The majority of commensal bacteria consist of gram-negative bacteria, such as Bacteroidetes, and gram-positive bacteria, such as Firmicutes [8, 9]. Gut bacteria such as Bifidobacterium can help in the production and supply of vitamins such as vitamin K and the water-soluble B vitamins [11]. The phyla Firmicutes and Bacteroidetes produce SCFAs from indigestible carbohydrates through collaboration with species specialized in oligosaccharide fermentation (e.g., Bifidobacteria). SCFAs are major anions in the colon, mainly as acetate, propionate, and butyrate. Butyrate is a primary energy source for colonic epithelial cells. Butyrate is consumed mainly by the colonic epithelium, and acetate and propionate will then become available systemically. The levels of SCFAs are significantly decreased in IBD, which may be a key factor that compromises intestinal and immune homeostasis [8]. Gut microbiota also play a very vital role in the growth of the host's immune system. A literature search has shown how one of the bacteria Candidatus Arthromitus, also known as segmental filamentous bacteria (SFB), alone promotes the maturation of the mucosal immune system [8, 13].

Any unfavorable alteration of the composition and function of the gut microbiota is known as dysbiosis, which alters the host–microbiota interaction and the host immune system [8]. Lately, many studies have been able to identify intestinal dysbiosis if present in patients with IBD, even though it still remains largely unknown whether the severity of gut dysbiosis is the cause of, or the response to, the severity of the disease [14, 15]. Studies summarizing the gut microbiota in patients with IBD compared with controls have consistently shown changes in microbiota composition as well as reduction in overall biodiversity [11]. IBD is associated with an increased abundance of Enterobacteriaceae, including *Escherichia coli* and Fusobacterium. It is also associated with

an increased abundance of Fusobacteriaceae, Pasteurellaceae, and Bifidobacteriaceae [11, 14]. These pathogenic bacteria have the ability to adhere to the intestinal epithelium, which in turn alters the diversity and composition of commensal microbes causing intestinal inflammation [8].

Role of Microbes

Several bacteria have been associated with the pathogenesis of IBD, including *Mycobacterium avium paratuberculosis*, enterotoxigenic *Bacteroides fragilis*, adherent/invasive *Escherichia coli*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Chlamydia* sp., *Aeromonas hydrophila*, *Salmonella typhi*, and *Clostridium difficile* (C. diff) [16–18].

Clostridium difficile

Clostridium difficile (*C. diff*) is a gram-positive, spore-forming, toxin-producing, anaerobic bacteria. Pathogenically, it primarily affects the colon, leading to either asymptomatic carriage or clinical disease that may range in severity from mild diarrhea to fatal pseudomembranous colitis, accounting for up to 50–75% of antibiotic-associated colitis [19, 20]. *C. diff* infections (CDI) are known to occur more frequently in patients with IBD, many of whom may not have had previous exposure to any antibiotics. Studies also show higher rates of asymptomatic carriage of *C. diff* of 8.2% (9.4% in patients with UC and 6.9% in patients with CD), versus 1% in healthy volunteers [21].

Toxins A and B (also known as TcdA and TcdB) are exotoxins that are thought to be major virulence factors of *C. difficile*. At least four functionally distinct domains of toxins A and B have been identified including the N-terminal region, enzymatically active glucosyltransferase domain, a cysteine protease domain, a hydrophobic segment, and C-terminal region with repetitive oligopeptide repeats (CROPs). Toxin A or B binds to the cell surface receptor with its C-terminus, followed by clathrin-mediated endocytosis of the toxin–receptor complex. A decrease in the pH inside the endosomal compartment leads to conformational changes within the toxins, permitting pore formation and translocation of the glucosyltransferase and protease domains into the cytoplasm. After activation, the cysteine protease domain autocatalytically cleaves the toxin to release the glucosyltransferase region, which inactivates the Rho family of proteins through glucosylation. Rho family of proteins is involved in intracellular signaling, and inactivation of Rho proteins in turn leads to disruption of the cell cytoskeleton and cell death. The inactivation of these proteins and cell death impairs the integrity of the membrane cytoskeleton and the barrier function of epithelial cells [22].

C. diff toxins have also been implicated in triggering a number of innate immune response pathways including NF-kB and MAP kinase. Exposure to toxin A leads to secretion on IL-8 by intestinal epithelial cells [23]. Studies suggest several other inflammatory cytokines are released in response to Toxin A and B including interleukin 18 (IL-18), IL-1beta, IL-6, and tumor necrosis factor (TNF-a). This alteration in the immune system with CDI may act as a trigger to IBD. A reduction in bile acids that occurs in IBD promotes *C. diff* growth and spore germination [22].

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped pathogenic bacterium that has been associated with chronic gastritis, peptic ulcer disease, and gastric malignancies [24]. *Helicobacter* species can be subdivided into two major lineages, the gastric *Helicobacter* species such as *H. pylori* and the enterohepatic (nongastric) *Helicobacter* species, which predominantly colonize the intestine and the hepatobiliary system. They have been linked to chronic liver and intestinal diseases [24]. In studies related to IBD, epidemiological evidence suggests negative correlations between the incidence of *H. pylori* and IBD [25].

A possible mechanism for the protective role of *H. pylori* in the development of IBD may be an alteration of the host immunologic response away from the pro-inflammatory T-helper (Th1/Th17) response toward an increased T-regulatory cell immune response, by increasing the expression of forkhead box P3 (FOXP3) [26, 27].

Listeria

Listeria monocytogenes (*L. monocytogenes*) is an intracellular gram-positive bacteria identified in 0.8–3.4% of the asymptomatic population on stool analysis [28]. It has been associated with infections in the central nervous system and bacteremia in patients with immunodeficiency, children, elderly, pregnant females, as well as healthy people [29]. Several studies have investigated the affinity between IBD and *L. monocytogenes*. It is presumed since patients with IBD receive immunosuppressive drugs, the defensive barrier in the gut is compromised, thereby making patients vulnerable to the colonization of *L. monocytogenes* [30].

Mycobacterium avium Complex and Paratuberculosis

Mycobacterium avium subspecies *paratuberculosis* (MAP) is an obligate pathogenic organism, linked to Johne's disease in cattle. Dalziel in 1913 first postulated the hypothesis of a link between Crohn's disease (CD) and MAP even before CD was described as he noted the similarities with Johne's disease, an intestinal disorder of cattle, and IBD in humans [31]. MAP causes chronic granulomatous ileitis (Johne's disease) in cattle and sheep, similar to some pathological features seen with CD. Olsen et al. showed an increased presence of MAP-reactive T cells that were extremely reactive to MAP and produced the pro-inflammatory cytokines Interferon-γ (INFγ) and Interleukin-17 (IL17) [32].

CD patients commonly have circulating antibodies namely anti-*Saccharomyces cerevisiae* antibody (ASCA) [33]. The epitope for this antibody is a mannan with a specific mannose alpha of 1–3 mannose (Man alpha1–3Man) terminal disaccharide. MAP is a possible source for the ASCA mannan epitope, and probably releases a mannose-containing glycoconjugate that inhibits killing of phagocytosed *E. coli* by macrophages, thus causing an indirect pathogenic mechanism for CD [34]. Nucleotide-binding oligomerization domain-containing protein 2, also known as caspase recruitment domain-containing protein 15 (NOD2/CARD15) receptors mutations, is known to be associated with increased rates of intracellular survival of the bacteria, eventually causing infection, due to abnormal development of Peyer's patches [35, 36]. Mutations in Nramp1 (natural-resistance associated macrophage protein 1) have been associated with an increased risk of mycobacterial infections, and polymorphisms in the Nramp1 promoter have been identified in patients with IBD [37]. It has also been hypothesized that even though MAP infects a large population, it only becomes pathogenic in individuals who are genetically susceptible due to an underlying genetic deficiency causing dysfunctional IFNγ activity [38].

E. coli

E. coli is a facultative gram-negative aerobe that has been found to be the numerically most dominant bacteria in the gut microbiota [39]. The association of *E. coli* with IBD was first suggested in 1978 when Tabaqchali et al. noted high titers of antibodies against *E. coli* O-antigens in patients with IBD [40]. *Escherichia coli* (*E. coli*) strains are classified into the following categories: A, B1, B2, C, D, E, and F phylogenetic groups. Group A and B1 are mainly commensal strains, while B2 and D groups are mainly pathogenic strains. Patients with IBD compared to the healthy individuals have been reported to have increased amounts of B2 and D strains of *E. coli* [41–43]. *E. coli* isolates from patients with IBD show increased adherence to gastrointestinal epithelial cells and are called adhesive and invasive *E. coli* (AIEC). AIEC have been shown to promote release of the pro-inflammatory cytokine IL-8 [44]. AIEC strains also result in increased expression of cell adhesion molecules; such as carcinoembryonic antigen related cell adhesion molecule 6 (CEACAM6) to promote bacterial colonization in the intestinal mucosa [45]. Studies have shown that certain genes promoting virulence are overrepresented in AIEC relative to nonpathogenic *E. coli*, namely, k1 and kpsm2 (effective in capsule synthesis), FynA, yersiniabactin, chu operon (utilized in iron metabolism), and ibeA gene (involved in invasion) [46, 47].

Campylobacter concisus

Campylobacter concisus (*C. concisus*) is a gram-negative, fastidious aerobic bacterium that normally colonizes the human oral cavity [48]; however, few studies found a significantly higher intestinal prevalence of *C. concisus* in patients with CD [49–51]. Strains of *C. concisus* have been shown to express a zonula occludens toxin (Zot) acquired likely through a CON-Phi2 prophage (a mechanism similar to Vibrio cholerae toxin), which enhances permeability of the epithelial cells [52]. Studies have shown an increased prevalence of Zot gene in *C. concisus* strains isolated from IBD patients [53].

Chlamydia pneumoniae

Chlamydia pneumoniae is a gram-negative rod suggested to have a higher prevalence in IBD patients. Mutations in the NOD2/CARD15 receptor have been studied as possible pathogenic mechanism for this bacterium. This mutation can cause activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) pathway, react with basic myelin protein in the immune system, and potentially trigger an autoimmune response [54, 55].

Mycoplasma pneumoniae

Mycoplasmas are small bacteria without a rigid cell wall, existing as either commensals or pathogens. Mycoplasmas are thought of as organisms of ubiquitous distribution with the potential to cause inflammatory diseases. M. pneumoniae

Table 37.1 Role of microbes and possible pathogenic mechanisms

Pathogen	Possible mechanism of action	References	Strength of evidence
Clostridium difficile	Toxin A- or B-related endocytosis releasing the glucosyltransferase region, which inactivates the Rho family of proteins → cell cytoskeleton and cell death. Trigger immune pathways including NF-kB and MAP kinase Release Interleukin 18 (IL-18), IL-1beta, IL-6, and Tumor necrosis factor (TNF-a)	[22, 23]	Likely a strong association, several studies available in literature
Helicobacter pylori	Alteration of the host immunologic response leading to an increased T-regulatory cell immune response Increasing the expression of forkhead box P3 (FOXP3)	[26, 27]	Likely a moderately strong association, few studies available in literature
Listeria monocytogenes	Excessive colonization of *L. monocytogenes*	[30]	Possible weak association, only a few studies available in literature
Mycobacterium avium subspecies *paratuberculosis*	Source for the ASCA mannan epitope, to release a mannose-containing glycoconjugate that inhibits killing of phagocytosed *E. coli* by macrophages: an indirect pathogen Inherent mutations or alteration in NOD 2/CARD 15, Nramp1, or IFNγ activity	[34–38]	Likely a strong association, several studies available in literature
Escherichia coli	Release pro-inflammatory cytokine IL-8. Increased expression of cell adhesion molecules, such as CEACAM6 Overexpression of virulent genes: k1, kpsm2, FynA, yersiniabactin, chu operon, and ibeA gene	[44–47]	Likely a strong association, several studies available in literature
Campylobacter concisus	Zot enhances permeability of the epithelial cells	[52, 53]	Possible weak association, only a few studies available in literature
Chlamydia pneumoniae	Mutation in NOD2/CARD15 receptor causes activation of NF-KB pathway, react with basic myelin protein and trigger autoimmune response	[54, 55]	Possible weak association, only a few studies available in literature
Mycoplasma pneumoniae	Increased production of IL-2, 4, 6, 8 Increased production of hydrogen peroxidase and superoxide radicals → damage to epithelial cells	[57, 58]	Possible weak association, only a few studies available in literature
Fecal Bacteria	Decreased numbers of *Faecalibacterium prausnitzii* and bifidobacteria	[61, 62]	Likely a moderately strong association, few studies available in literature

DNA was detected at a significantly higher rate in intestinal biopsies from patients with CD, suggesting some role in the pathogenesis of IBD [56]. Possible pathogenic mechanisms associated with Mycoplasma include increased production of various regulatory cytokines (IL-2, IL-4) and inflammatory cytokines (IL-6, IL-8) [57] as well as increased oxidative stress due to increased production of hydrogen peroxidase and superoxide radicals resulting in damage to epithelial cells [58].

Fecal Bacteria

Several studies have suggested an alteration in the relationship of commensal bacteria in the intestine and host immune system as a possible pathogenic mechanism in IBD [59, 60]. 95% of the bacteria in stool samples from healthy adults belong to the Bacteroides, *Clostridium coccoides*, and *Clostridium leptum* subgroup [61]; however, IBD patients have lower numbers of these organisms, including bifidobacteria but, in particular, the *C. leptum* subgroup. Studies have found a strong association between ileal CD and lack of *Faecalibacterium prausnitzii*. *F. prausnitzii* has anti-inflammatory effects on Caco-2 cells, as metabolites secreted by this bacterium blocks NF-kappa B activation and IL-8, 12 and IFN-gamma secretion, and promotes secretion of anti-inflammatory IL-10 [62] (Table 37.1).

Animal Models of Intestinal Inflammation

Several types of models for colitis are available including genetically driven, chemically induced or immune mediated, all of which are represented in mouse models of colitis. Some of the examples of genetically driven models available are interleukin-10 (IL-10) deficient mouse, resulting in uncontrolled inflammation in the gut [63, 64], the *Mdr1a*$^{-/-}$mouse, deficient in P-glycoprotein 170, resulting in increased gut permeability, microbial translocation and colitis development [65], the SAMP1/YitFc mouse, which develops spontaneous ileitis [66], and the TRUC mouse, where deficiency in both *T-bet* and *Rag2* causes increased TNFα responses [67].

Models that are developed by immune activation include the T cell transfer model, where naive T cells are transferred into a lymphopenic recipient mouse, that may result in wasting disease, prevented by cotransfer of regulatory T cells [68, 69] and anti-CD3ε monoclonal antibody model, in which T cell activation results in intestinal mucosal damage and a cytokine storm [70, 71]. *Citrobacter rodentium* or rotavirus can cause intestinal inflammation, and is used as a model to study the inflammatory response [72–75]. Models with chemically induced colitis include administration of compounds that cause epithelial damage, for example, dextran sulfate sodium (DSS), piroxicam or 2,4,6-trinitrobenzene sulfonic acid.

Management

Options Targeting Microbes

A variety of therapeutic options have emerged to target microbes in IBD. These include probiotics, prebiotics, antibiotics, fecal microbiota transplantation (FMT), and dietary changes.

Probiotics are live microorganism preparations thought to promote human health; they have been studied in IBD with the theory that they might work to improve the balance in the gastrointestinal microbiota, thereby reducing intestinal inflammation. The mechanism by which this could occur may be due to less colonization resistance, better intestinal barrier function, signal transduction alteration, and metabolic effects [76]. Different preparations of probiotics have been used in studies. VSL#3, a combination of eight different lactic acid bacteria, has been used in numerous studies [77–81]. Other formulations include Nissle 1917 (a nonpathogenic *E. coli* strain), Lactobacillus GG, Bifidobacteria-fermented milk, and Bifidobacterium longum/Synergy [82–89], among others. Additionally, probiotic therapy has been studied in pouchitis, a known possible complication after surgical reconstruction in IBD patients [90].

Gut microbiota is affected by dietary intake. A similar concept to probiotics in the treatment of IBD is the use of prebiotics, which have been suggested to provide a metabolic substrate to promote the proliferation of beneficial microbes [91].

Fecal microbiota transplantation is another potential therapeutic option to alter gut dysbiosis in IBD. In FMT, fecal flora from a healthy person is transplanted to the diseased. This therapy has been shown to be efficacious in resolution of *C. difficile*-associated diarrhea and is now used in clinical practice as a treatment option [92]. If IBD is the result of dysbiosis, it is thought that FMT from a healthy donor may be able to restore symbiosis, similar to the outcomes found in *C. difficile* infection resolution.

Antibiotics have widely been used to treat acute and chronic pouchitis and fistulizing disease [93]. Ciprofloxacin and/or metronidazole are used in perianal CD in conjunction with other medications such as biologics [94]. Azithromycin and rifaximin have also been used to treat mild to moderate luminal CD. The theory behind the use of antibiotics is to eradicate potentially pathologic gut microbes. Use of antibiotics has been with caution, however, due to the concern of creating an imbalance in commensal organisms such as the case with the potential for development of pathogenic *C. difficile* colitis. A systematic review and meta-analysis of 22 studies showed significantly higher rates of CDIs in patients with CD involving their colon [95]. There was also an association with CDIs in those who used antibiotics within the last 30 days and in those using biologic medications.

Evidence, Efficacy, and Prognosis

Lactobacillus casei, a probiotic, has been shown in a study to downregulate pro-inflammatory cytokines in Crohn's disease thereby antagonizing the inflammatory effects of host *E. coli* [96]. Several studies have explored this concept in mouse models. An example is C. rodentium-induced colitis in mice, which was lessened by the use of *Saccharomyces boulardii*, a probiotic [97]. Another example is the use of probiotics to reduce gut inflammation by means of modulating growth factors to promote epithelial restoration [98].

Several studies using VSL#3 in UC patients have shown it to be efficacious in both induction of remission as well as use in maintenance therapy [77–81]. Prevention of recurrence of chronic, relapsing pouchitis with the use of VSL#3 was shown in two double-blinded placebo-controlled trials [77, 78]. When VSL#3 was added to standard therapy (mesalazine and steroids) in 29 pediatric patients with UC, remission rates at 4 weeks were 92.8% compared to 36.4% in placebo [81]. When they looked at recurrence rates 1 year later, the VSL#3 group was 36.4% vs. 73.3% in the placebo. A study in patients with UC who underwent ileal-pouch-anal-anastomosis involved 4 weeks of daily lactobacilli and bifidobacteria administration to 51 UC patients. Stools samples showed an increase in the number of these bacteria during intervention as well as a decrease in involuntary defecation, leakage, abdominal cramps, fecal number, consistency, and mucus, and urge to evacuate stools [90]. Lactobacillus, Bifidobacterium, and *Saccharomyces boulardii* in combination, as well as Nissle 1917, were found to induce and maintain remission in moderately severe UC [99].

One of the first studies using FMT dates back to 1989, when an author of the paper, with UC, received FMT and

reported disease-free remission [100]. In 2012, a systematic review showed 13 out of 18 patients with UC who achieved remission with FMT [101]. There is some conflicting evidence in other studies; two longitudinally prospective studies of FMT therapy in UC patients did not achieve clinical remission [102, 103]. There was suggestion in these studies that in most patients, the gut microbiota was indeed altered, albeit temporarily, and so may require repeat FMT therapy at periodic intervals to sustain disease remission. Additionally, there may be specific organisms which confer worse success with FMT when overrepresented in the gut flora as compared to other organisms [102]. This might be an important factor in determining which individual is more likely to respond to FMT. A more promising study of 10 UC pediatric patients showed a 79% clinical response rate to FMF therapy within 1 week [104]. A more recent meta-analysis and systematic review of 29 studies and 524 FMT-treated IBD patients has shown a concerning alternative outcome—IBD flaring after FMT [105]. The rates of IBD worsening were higher with lower GI FMT delivery as opposed to upper GI delivery, suggesting a possible site variance (16.5% vs. 5.6%). The rates of worsening were considered to be marginal (4.6%) and it was questioned as to whether it was due to other etiologies.

Prebiotic data is limited, but as of a 2014 review, had yet to show any effect as a therapeutic option in IBD [91].

It appears that the data have been conflicting regarding the use of antibiotics in CD and UC. A meta-analysis made the conclusion that antibiotics were superior to placebo in inducing remission [91]. Another had a similar encouraging conclusion that antibiotic therapy induced remission and prevented relapse in IBD patients [106]. As stated previously, however, the risk of developing a CDI is increased in those with IBD and increased in those IBD patients who used antibiotics within the last 30 days [95].

As stated by Aleksandar et al. in their work on the microbiome in IBD, there is no certain diet in IBD patients which has been shown to cause, prevent or treat this disease [107]. However, Enterobacteriaceae have been shown to be increased in IBD, and one study showed, in long-term strict vegan diets, a significant decrease in Enterobacteriaceae, as well as *Bacteroides* spp. and *Bifidobacterium* spp. [108].

In review of the variety of therapeutic options to target microbes in IBD, it appears that some have shown more promise than others and all require more data to be able to draw more solid conclusions. A significant amount of work seems to be focused on the use of probiotics and more is emerging for the use of fecal microbiota transplantation as well. Probiotic data is encouraging while FMT data is conflicting. At this time, it does not seem that any particular diet is definitely efficacious nor are prebiotics. These findings are summarized in Table 37.2.

Table 37.2 Summary of management options targeting microbes

Microbe target	Evidence	Reference
Probiotics	Encouraging, mostly in UC and pouchitis	Matsuoka, [2–6, 19–22, 109, 110]
Fecal microbiota transplantation (FMT)	Conflicting, may be transient effect	[23–28]
Prebiotics	No clear effect	[111]
Antibiotics	Conflicting	[18, 29, 111]
Diet	No clear effect	[30]

Discussion and Future Direction

As highlighted in detail above, gut microbiota are an exciting target to study and are likely to reap rich rewards in furthering our understanding of initiation and perpetuation of chronic IBD. However, there is a complex relationship between the gut immune system and the microbiota. Accumulating evidence also suggests that the dynamic balance between microbes, particularly commensal flora, and host defensive responses at the mucosal frontier has a pivotal role in the initiation and pathogenesis of chronic IBD. However, it remains unclear whether the dysbiosis observed in IBD is a cause or a consequence of intestinal inflammation. It still remains unclear how dysbiosis regulates the gut immune system. Hence, further research into this relationship is not only likely to give us better insight into it but is almost necessary to improve outcomes of chronic IBD.

It is also important to note that the etiopathogenesis of chronic IBD is complex, multifactorial, and a combination of genetic predisposition and environmental exposures, and the gut microbiota play significant roles. Among genetic factors, NOD2 has remained the strongest genetic risk factor associated with chronic IBD development for nearly two decades, although exactly how it is related to disease onset remains elusive. Important environmental risk factors for the pathogenesis for IBD include smoking, diet, antibiotics, and OCPs. Among these, smoking has been best studied and has shown a clear association with chronic IBD. Also important is the hygiene theory, which can explain unknown environmental exposures that may interact with the immune system and result in an abnormal inflammatory response to intestinal microflora.

Several bacteria have been associated with the pathogenesis of IBD and remain the focus of research in furthering the understanding of their role in chronic IBD. The gut microbiota is composed not only of bacteria but also of viruses and fungi which also likely contribute significantly to IBD. The role of these should also be studied in detail. The role of gut microbiota is being suggested strongly by the analysis of mouse models and has revealed at least two major courses of disease: dysbiosis (involving the depletion or alteration in resident species, which can be followed by

loss of colonization resistance, acute infection by bacteria that can breach the intestinal barrier, then possibly develop into chronic inflammation) and chronic pathogen infection (which can be aggravated by the presence of commensals because barrier disturbances and immunomodulation can increase immune responses to resident bacteria). The most likely pathogens remain elusive but there are a number of candidate pathogens that may have a strong contribution to the development of chronic IBD. Further efforts to identify pathogens that are commonly associated with human disease and the potential protective microbiota, depletion of which might aggravate disease, can provide clarification on these issues. The likely candidate pathogens include enterotoxigenic *Bacteroides fragilis*, *Clostridium difficile*, *Helicobacter* spp. and *Campylobacter* spp. and should be further investigated. An exciting candidate is *Mycobacterium avium* subspecies paratuberculosis, which has received considerable attention as a possible trigger of human IBD.

Unfortunately, our understanding of the microbial flora itself is quite incomplete. Insights into the microbial–host interrelationships are hampered by both the limited knowledge of the diversity and complexity of the microbial flora and the limitation of available tools to delineate these characteristics. Metagenomic and computational analysis of the so-called microbiome may provide a foundation to achieve an understanding of the relevant, functional diversity of the flora in the context of IBD. Understanding the distribution, dynamics, and responses to microbial flora in these disease states will probably provide insights into a number of aspects of IBD.

Since gut microbiota are such an exciting target in understanding of chronic IBD, a number of therapeutic strategies have been tried to target them. These include probiotics, prebiotics, antibiotics, fecal microbiota transplantation (FMT), and dietary changes. It is very clear that antibiotics are not efficacious and are possibly harmful in this context. Dietary changes and prebiotics also do not seem to work. Probiotics and fecal microbiota transplant remain promising. Probiotics have been shown to be efficacious and tend to be well tolerated with minimal downside. They should be considered in appropriate patients with chronic IBD. On the other hand, the role of FMT in the therapy of chronic IBD remains unclear, and various studies have provided conflicting results including raising concern for possible worsening of the disease. This may be due to the study design, the selection of population, and unclear standardization of the FMT procedure.

All of the above developments highlight the role gut microbiota plays in chronic IBD, and it is our belief that we have only scratched the surface of our understanding of this role.

Summary

The main factors playing a role in IBD are genetic, environmental, gut microbiota, and immune response. Among these, gut microbiota influences every aspect involved in causation and perpetuation of the disease with complex interactions among these factors. Yet, it remains elusive how a single agent or a short list of agents exerts a majority of this influence. The use of probiotics and fecal microbiota transplant to impact the gut microbiota looks promising but unproven. Nonetheless, gut microbiota represents a "gold mine" for both clinical and basic IBD research and this is an exciting time of discovery; breakthroughs are likely to come soon in this area.

Conflicts of Interest The authors have no conflicts of interest.
There was no funding for this book chapter.

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Part V

Management of Rheumatic Disorders

Infections in Systemic Lupus Erythematosus

38

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Abbreviations

cGAS	Cyclic GMP-AMP synthase
CHIKV	Chikungunya virus
CMA	Cardiac muscle antibodies
DAH	Diffuse alveolar hemorrhage
DC	Dendritic cells
EBV	Epstein-Barr virus
HAART	Highly active antiretroviral therapy
HPV	Human papillomavirus
IRIS	Immune reconstitution inflammatory syndrome
MBL	Mannose-binding lectin
MeSH	Medical Subject Headings
SHS	Strongyloidiasis hyperinfection syndrome
TLRs	Toll-like receptors
ZIKV	Zika virus

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Introduction

Despite the important advances that we have made in the pathogenesis, diagnosis, and treatment, as well as in the increase in the survival of systemic lupus erythematosus (SLE) patients, infections remain one of the main causes of morbidity and mortality in our patients [1].

Multiple environmental and biological factor characteristics of SLE, such as profound alterations in immunoregulation, play an important role in susceptibility to infections. Additionally, treatments such as steroids and immunomodulators, as well as new treatments, will contribute to the development of infections by common and opportunistic infectious agents [2].

Environmental factors such as food, health conditions, pollution, socioeconomic conditions, as well as genetic polymorphisms and epigenetic changes can modify the clinical expression of SLE and the susceptibility to viral, bacterial, fungal, and parasitic infections [3].

The interaction of any of these infectious agents with the organs and systems of a patient with SLE will modify the clinical picture. The presence of fever as a sign of infection or activity of SLE, as well as the use of antibiotics, steroids, or immunomodulators, will always be a diagnostic and therapeutic challenge. The difference between SLE flare and infection will require a high degree of clinical judgment and the adequate use of the biomarkers that we currently have [4–6].

This chapter will review the current situation of infections in SLE, its impact in different regions of the world, the most frequent infectious agents, as well as the interactions between infectious agents and the immune system, differential diagnosis between reactivation of SLE and infection, and the strategies to be followed to decrease the morbidity and mortality caused by infections.

Epidemiology of Infections in SLE

Systemic lupus erythematosus (SLE), a chronic and multisystem autoimmune disease, is recognized worldwide; however its clinical expression is very diverse, due to the existence of a

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_38

variety of environmental factors, which interact with genetic risk factors to develop SLE. One of the most important environmental factors is infections, which will interact with SLE patients and modify their clinical course and treatment. In this way, the incidence and prevalence of infections in SLE allows to better understand the impact of infections on the morbidity and mortality of SLE patients. However, these epidemiological data may vary from country to country, even from continent to continent, due to the variety of infectious agents and the socioeconomic conditions of each place.

The incidence of infections in SLE was analyzed in the last century. From 1966 to 1976, an infection rate of 59 per 100 patient-years was found in the USA in 223 patients with SLE. The most frequent infections were bacterial, viral, and opportunistic germs [7]. In the 1980s, an epidemiological study conducted in Sweden found in a group of SLE patients an infection rate of 142 per 100 patient-years, with a predominance of viral and bacterial infections. The activity of the LES and the doses of steroids were factors associated with these infections [8]. In the decade of the 1990s, a multivariate analysis of the survival of 389 patients with SLE in the USA showed that thrombocytopenia was an independent factor of poor prognosis, especially in African-Americans, and infections were the main cause of death in all groups studied [9]. Other studies conducted in different countries confirmed that infections are the main causes of morbidity and mortality in SLE, especially in hospitalized patients [10]. It is considered that the prevalence of infections in hospitalized patients is from 10% to 35% and the mortality varies from 29% to more than 50% [5]. Most of these studies come from research conducted in developed countries. In this regard, we consider that there is an under-registration of infections in patients with SLE in developing countries. To support this idea we have made a systematic search in PubMed database from January 2008 to October 2018, including original articles, reviews, editorials, and letters to the editor. The Medical Subject Headings (MeSH) system was used, considering the words "systemic lupus erythematosus" and "infection." We excluded abstracts from congresses, corrections, and notes. A total of 202 articles that fulfilled the selection criteria were included. Case reports and original works were the most published articles (110 and 66, respectively). The United States of America, China, Japan, Brazil, Spain, India, Mexico, Israel, South Korea, and Canada were the most productive countries. Figure 38.1 and Table 38.1 summarize these findings.

Fig. 38.1 This map shows the number of publications about infections and SLE. There is a bias related to publications, due to the under-registrations and few investigations in developing countries

Table 38.1 Infections and SLE publications 2008–2018

Country	Number of publications
United States of America	29
China	22
Japan	15
Brazil	12
Spain	11
India	9
Mexico	8
Israel	7
South Korea	7
Canada	7
United Kingdom	6
Taiwan	6
Thailand	5
Italy	5
France	5
Portugal	4
Greece	4
Colombia	3
Argentina	3
Saudi Arabia	3
Netherlands	3
Philippines	3
Malaysia	2
Germany	2
Tunisia	2
Morocco	2
Denmark	2
Croatia	2
Turkey	2
Egypt	1
Peru	1
Iran	1
Singapore	1
South Africa	1
Sri Lanka	1
Ghana	1
Jamaica	1
Uruguay	1
Nepal	1
Lebanon	1
Total publications	202

Risk Factors for Infections in SLE

Several risk factors for the development of infections in patients with SLE have been identified [11]. The risk factors described can be divided into those related to SLE, the use of immunosuppressive/immunomodulatory drugs, and alterations in immunoregulation (Table 38.2). However, these risk factors have been identified in diverse populations around the world, in different clinical contexts and study designs.

Recent data from a Spanish registry of 3658 patients with SLE was published. At least one episode of serious infection was observed in 19.3% of patients. The authors found that age at diagnosis, Latin American ethnicity, use of glucocorticoids (>10 mg/day), use of immunosuppressants (rituximab, abatacept, and mycophenolate mofetil), hospitalization due

Table 38.2 Risk factors described for infection in patients with SLE

Disease-related factors	Lupus nephritis [17] High activity of lupus [12, 13] Lymphopenia [21, 31, 32] Thrombocytopenia [17] Anemia [21] Hypoalbuminemia [21] Accrued damage [12]
Drugs	Glucocorticoids [12, 14, 17, 21, 24] Immunosuppressive drugs [15, 18] Biologic therapy [12, 16]
Intrinsic immune dysregulations	Diminished chemotaxis to IL-8 [26] Impaired phagocytosis [27, 29] Low production of reactive oxygen species [28] Low serum mannose-binding lectin levels [30] T cell alterations [27] Hypogammaglobulinemia [27] Low complement levels [13, 24, 31, 55]
Other	Smoking [12] Hospitalization [12, 13, 24] Ethnicity [12]

to SLE, severity of the disease, rate of chronic damage, and smoking were factors associated with the development of severe infections, and it confirms the use of antimalarials as a protective factor [12]. In a retrospective study of 142 patients hospitalized with SLE, an incidence of infections of 50.7% was found. In this population of Chinese patients, alterations in leukocytes, high levels of C-reactive protein, low levels of C4 complement, and prolonged hospitalization (>14 days) were found to be independent risk factors for infection [13].

As previously noted, several drugs used to treat SLE have been associated with the development of infections. In a historical cohort study that included 3030 patients with SLE, an increased risk of serious infections was found in those new users of glucocorticoids without antimalarials. On the other hand, the use of antimalarials seems to reduce this risk [14]. In a nationwide longitudinal study of Medicaid SLE patients, no differences were found in first serious infection rates in new users of azathioprine, cyclophosphamide, or mycophenolate mofetil, although, globally, the use of these immunosuppressants increases the risk of infections [15]. Biological drugs such as rituximab and abatacept have also been linked to an increased risk of infections in patients with SLE. In a retrospective study of 101 Asian lupus nephritis patients hospitalized for some episode of infection, it was found that the use of rituximab was a predictor of hospital admission for an infection [16].

Although the factors associated with the development of infections by different microorganisms overlap, some studies have shown some differences. In a study of 3815 Chinese SLE patients hospitalized, 34.6% of them had an infection. High activity of the disease, renal involvement, thrombocytopenia, high doses of glucocorticoids, and treatment with cyclophosphamide were factors associated with bacterial or

viral infections. Whereas lupus nephropathy, high doses of glucocorticoids, and treatment with cyclophosphamide were factors associated with fungal infection [17].

Risk factors for infection have also been studied in specific situations. Lupus nephritis is one of the manifestations of the disease associated with increased morbidity and mortality. In a systematic review and meta-analysis of 32 controlled clinical trials involving 2611 patients with lupus nephritis, it was found that the use of cyclophosphamide at low doses, cyclophosphamide high dose, and glucocorticoids was associated with an increased risk of developing serious infections in comparison with the use of tacrolimus [18]. Diffuse alveolar hemorrhage (DAH) is a rare complication of SLE but potentially fatal associated frequently with infections. In a multicenter study of 56 episodes of DAH in 50 patients, infection was found in 38.6% of the cases. Infections were associated with treatment for SLE, mechanical ventilation, hypocomplementemia, and high levels of C-reactive protein [19]. Patients with SLE have a higher risk of developing complications in orthopedic surgery, including infections [20]. In a retrospective cohort study of patients with SLE undergoing major surgery, it was found that the use of prednisone, the presence of anemia, hypoalbuminemia, and lymphopenia were variables associated with the development of infectious complications [21]. Mortality related to infection in patients with SLE is observed in around 30% depending on the population studied [22]. In a cohort study of 125 patients with SLE and infections, 11.2% of deaths related to infections were observed. The authors found that SLE activity and bacteremia were independent risk factors for infection-related mortality; the use of hydroxychloroquine, meanwhile, was a protective factor [23]. In addition, this mortality is increased by the development of multidrug-resistant strains. In this regard, a retrospective case-control study of patients with SLE found that the C3 low complement prior to infection, hospitalization history, and dose of prednisone were independent risk factors for the development of bacterial infections resistant to drugs [24]. Several defects of immunoregulation described in patients with SLE have been associated with an increased susceptibility to infections [11, 25]. Various defects in neutrophils from patients with SLE have been described, including defects in chemotaxis, phagocytosis, and oxidative stress [26–28] (Table 38.2). Recently, an in vitro study demonstrated that low complement levels in the blood of patients with SLE lead to downregulated opsonophagocytosis of bacteria by healthy neutrophils [29]. Other components of the innate immune response have also been related to infections in patients with SLE, such as the complement system, especially the activation pathway of lectins. Low serum levels and various allelic variants of mannose-binding lectin (MBL) have been associated with infections in patients with SLE [30]. However, other authors have not found the same results. Alterations in the adaptive immune response have also been associated with the development of infections in patients with SLE. Lymphopenia is a distinctive alteration of SLE and has been associated with infections [21, 31, 32]. More recently, in a case-control study, it was found that those hospitalized patients with SLE and infection had significantly lower levels of CD4+ T cells and CD4+/CD8+ ratio and significantly higher levels of CD8+ T cells compared to patients with SLE without infection. In addition, the concentrations of IgG in patients with infection were significantly lower than those in patients without it [27].

Immunological Disorders Caused by Infections in SLE

Autoimmunity is defined as a response of T and B lymphocytes against the antigens themselves without causing damage. This phenomenon becomes an autoimmune syndrome, when this normal response causes tissue damage, because the mechanisms of central immune response (thymus and bone marrow) and/or peripheral (lymphocytes) or anergy fail and allow self-reactive lymphocytes to survive and become active. In people with HLA-type or genetic predisposition, infections are a trigger factor for autoimmunity and autoimmune syndromes. Mechanisms such as molecular mimicry of infectious agents, immune activation by auto-epitopes, and bacterial superantigens act as trigger for polyclonal activation of T cells and autoimmunity. An example of mimicry is *Chlamydia* species that show similarity to myosin in the myocardium [33]. Environmental factors involved in SLE are the microbial superantigens that disrupt normal immune responses and cause the unbridled activation of nonspecific T cells that can lead to the proliferation of autoreactive T cells. Potent pyrogenic exotoxins as staphylococcal enterotoxin B and streptococcal pyrogenic exotoxin A might act as superantigens causing or aggravating autoimmune diseases. SLE has Th2 cytokine pattern, and recently a research of T cell phenotypes and cytokine secretion [Th1 (IL-2 and IFN-c) and Th2 (IL-4 and IL-10)] on in vitro stimulation with bacterial superantigens was done. They found expansion of CD4+ T cells and reduced percentages of CD8+ T cells by superantigens, indicating that reduced CD8+ T cells may lead to hyperactivity of CD4+ T cells due to reduction in regulatory check by suppressor CD8+ T cells in SLE patients [34]. Systemic lupus erythematosus and antiphospholipid syndrome could appear after acute or chronic intracellular invasion of *Coxiella burnetii*, called Q fever. Anti-*C. burnetii* IgG antibodies could decline even though if the infection persists; in contrast, anticardiolipin antibodies (aCL) appear in about half of cases. With less frequency other autoantibodies appear, including antinuclear antibodies (ANA), anti-dsDNA antibodies, and cardiac muscle antibodies (CMA) especially associated to myocarditis [33]. With respect to viral influences in autoimmunity, Epstein-Barr virus (EBV) is a gamma herpes virus associated with SLE. EVB remains in latency

in B cells over the immune response of the host given its homology with proteinases and human IL-10. Human IL-10 is a factor for B cell growth and differentiation and potent inhibitor of pro-inflammatory cytokines. Viral IL-10 is inefficient in the regulation of anti-inflammatory genes and stimulation to monocytes leads to less clearance of apoptotic cells compared to human IL-10. Therefore, altered innate immune function contributes to the persistence of EBV and greater opportunity to present autoantigens from dying cells phagocytosed by dendritic cells (DC). EBV induces loss of tolerance and amplification of autoimmune responses in patients with SLE [35]. On the other hand, activation of latent EBV could be responsible for production of type I interferon (IFN-I) playing a pathogenic role in SLE. Two receptors, Toll-like receptors (TLRs) and cytosolic nucleic acid sensors, are potentially relevant to the pathogenesis of lupus by amplifying the innate activation of the immune system. EBV can trigger TLR9 in a major histocompatibility complex (MHC) class II-dependent manner, activate TLR7, and stimulate IFN-I production. Dengue RNA mediates release of mitochondrial DNA, providing ligands for the cyclic GMP-AMP synthase (cGAS) pathway and induction of IFN-β. Malaria parasites activate macrophages by a signaling from cytosolic nucleic acid receptors and induce dendritic cells to respond through the TLR7 pathway, resulting in perpetuating IFN-I production, immune system activation, and tissue inflammation [36]. Surprisingly, in some cases, the infections have a protective effect, as occurs with helminthes infection, which have been used with success in prophylactic and therapeutic models of autoimmunity including SLE. Parasitic helminthes evade detection and expulsion by regulating host immune responses by-products such as ES-62 containing phosphorylcholine. Therefore, ES-62 helps to decrease the inflammatory response to antigens recognized as pathogen-associated molecular patterns. Nowadays, synthetic non-immunogenic small molecule analogues were designed searching to mimic ES-62's immunomodulation and promotion of B regulatory responses (Bregs) in models of SLE. Also, ES products from other trematodes such as *Fasciola hepatica* can generate a potent Treg response [37]. Products of collective genomes of commensal microbiota induce protective responses to pathogens and maintain the regulatory pathways of tolerance to harmless antigens, as well as the balance in the innate and adaptive immunity. Lupus mice had reduced *Lactobacillus* and anti-inflammatory *Bifidobacterium* but increased inflammatory *Lachnospiraceae*. In human SLE, the gut *Firmicutes*/*Bacteroidetes* ratio is lower compared to healthy people, even though of similar total bacteria. Other researchers found that SLE microbiota promotes lymphocyte activation and Th17 differentiation and may influence the development of specific manifestations of lupus or disease flares [38]. In this way all viruses, bacteria, parasites, and all microorganisms with which our immune system interacts can potentially modify the balance between tolerance, normal defense, and autoimmunity. Figure 38.2 shows the main mechanisms of interactions between infectious agents

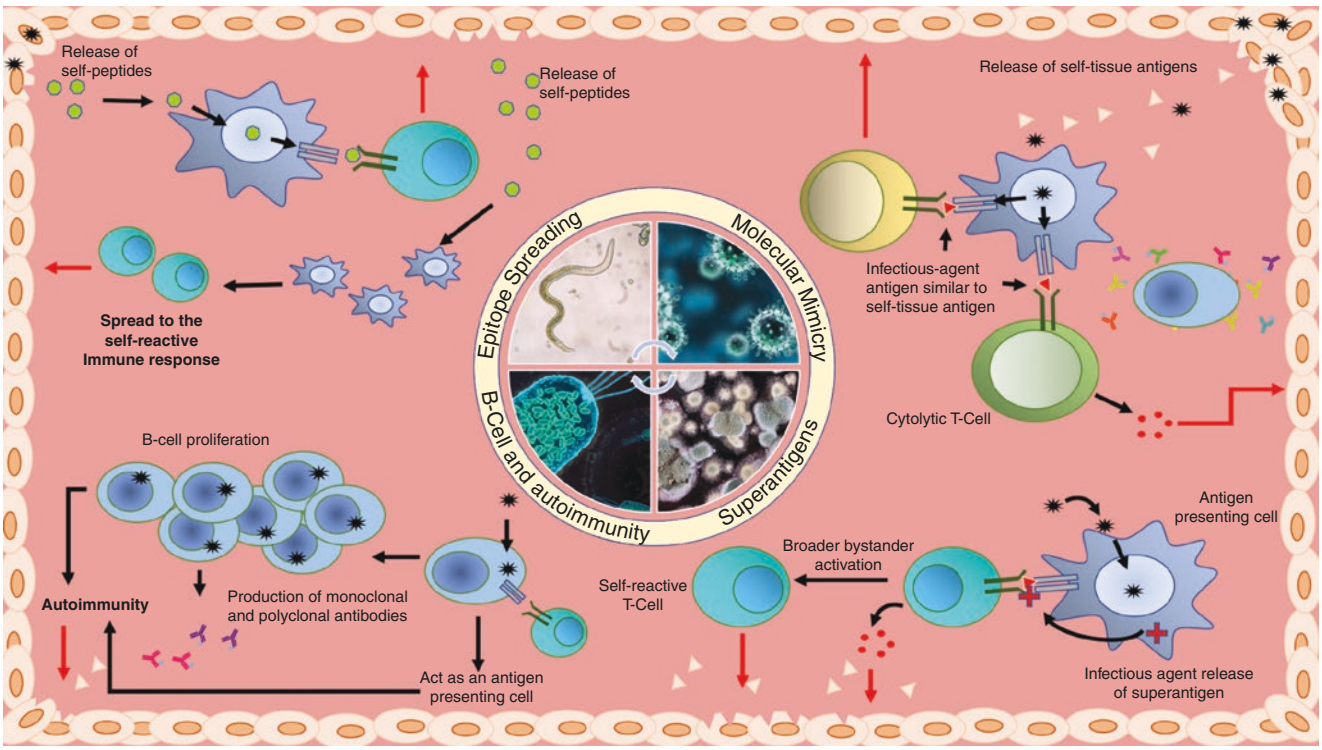

Fig. 38.2 Interactions between infectious agents and immune system in SLE patients. On the right side, molecular mimicry and superantigens; on the left side, epitope spreading and B cell activation

and immune system in SLE patients: (1) molecular mimicry, (2) superantigens, (3) epitope spreading, and (4) B cell activation.

Specific Types of Infection in SLE

Infection continues being an important cause of mortality and morbidity in patients with SLE. The incidence of infections in patients with SLE varies according to the population, between 50 and 150 episodes for every 100 patients/year [39]. Bacterial infections are the most frequent, followed by viral and fungal infections. In this section we will analyze the main infectious processes associated to the disease.

Bacterial Infections

These are the most common agents, being the respiratory, digestive, urinary tracts, soft tissues, and skin the usual sites of infection [11]. Urinary and skin infections are more common in outpatients; on the contrary, respiratory infections are most prevalent in hospitalized patients [40, 41]. Bacterial lipopolysaccharides or nucleic acid-containing immune complexes alter the immune system. Bacterial products bind to TLRs or other receptors on antigen-presenting cells, B cells, and T cells. These interactions activate immune cells leading to production of proinflammatory cytokines and innate immunity activation. On the other hand, TLR ligands stimulate plasmacytoid dendritic cells to produce IFN, giving place to the release of autoantibodies. Furthermore, cellular debris produced by bacteria such as nuclear components can act as autoantigens [42]. Common bacterial pathogens include *Streptococcus pneumonia* in respiratory infection, *Staphylococcus aureus* that induces skin, soft tissue, bone, and joint infections as well as bacteremia, and *Escherichia coli* that is the most common pathogen causing urinary tract infection; *Klebsiella* and *Pseudomonas* spp. are other pathogens in urinary tract infections. *Salmonella* has also been identified as causing bacteremia in patients with SLE, which by itself has also been reported as a frequent predisposing condition for the development of bacteremia [42]. In patients with lupus nephritis bacteria are identified as the main source of infections; however it may vary according to epidemiological and clinical settings. In a Chinese study analyzing death causes from the past 24 years, patients who died had mixed infections more commonly than single pathogen infections, fungal infections being the most predominant [43]. In Latin American patients, the GLADEL study revealed disease activity plus infection as the main cause of death (44%), followed by SLE activity alone (35%), and infection alone (15%) [44].

Tuberculosis

Regarding tuberculosis (TB) its incidence varies depending on the region, but it seems to be higher in SLE patients than in the general population. The interplay between SLE and TB is complex. Tuberculosis is more prevalent in SLE patients and this infection may be a risk factor for the development of the disease. Furthermore, frequently TB in SLE patients is more extrapulmonary, with more widespread pulmonary involvement and with a higher relapse rate [45]. A study from Spain found that the incidence of TB was sevenfold higher in SLE patients in comparison with the general population [46]. A prevalence of TB around 5% has been calculated in SLE patients living in endemic areas [11]. A recent study in Southern China found that SLE patients are at high risk of TB, especially extrapulmonary and disseminated TB. Coinfection with other pathogens was also present. The accumulated doses of glucocorticoids as well as lymphopenia were associated with TB [47]. In a study in Mexico City 33% of tuberculosis cases were pulmonary only, 47.2% extrapulmonary alone, and 19.4% both. Cumulative dose of prednisone in SLE patients was associated with TB and the antimalarial treatment was protective [48]. High suspicion of TB in SLE patients from endemic countries must be taken into account, mainly in those with nephritis and high cumulative doses of corticosteroids.

Viral Infections

Several viral pathogens have been associated with SLE in different populations. The main association is with EBV, a member of the herpes virus family, infects B cells and is linked to SLE through molecular mimicry, bystander activation, and epitope spreading [49]. In a recent study around 98% of Chinese population was infected with EBV before 30 years of age and this infection was associated with SLE [50]. Piroozmand et al. [51] found that in addition to the high frequency of infection with EBV virus in SLE patients, viral load in patients with active lupus was higher than patients with inactive lupus, thus making evident the role of virus on activity and pathogenesis of disease. Human papillomavirus (HPV) infections have been reported among SLE patients. It has been found that a diversity of peptide overlaps between HPV, EBV, and HERV antigens and human proteins associated to SLE, supporting the hypothesis of cross-reactivity in SLE onset following these infections [52]. With respect to other viral infections such as Zika and Chikungunya virus (CHIKV) infections, SLE might cause arboviral coinfection-related morbidity/mortality and vice versa. Silva et al. [53] reported a case of both Zika virus (ZIKV) and CHIKV virus infection in a SLE patient with lupus nephritis that evolved to fatal outcome due to renal failure possibly resulting from the direct effect of these viruses, since renal tissues presented

virus particles. Nowadays, arboviral infections induce arthritis mimicking rheumatoid arthritis; however, little is known about these infections triggering or aggravating other rheumatologic diseases such as SLE.

Fungal Infections

Invasive fungal infections are an important emergent disease in SLE patients, with a prevalence varying from 0.83% to 4.8% in different populations. Its importance underlies in that the mortality risk increases in these patients in comparison with those without infection. These infections are caused by fungi such as *Cryptococcus* spp., *Aspergillus* spp., *Candida* spp., and *Histoplasma* spp., among others [54]. Risk factors for developing invasive fungal infections in SLE patients are a high score in systemic lupus erythematosus disease activity index (SLEDAI) 2 K (more than 8 points), neutropenia, lymphopenia, elevated titers of anti-DNA antibodies, use of steroids and antibiotics, mechanical ventilation, and hemodialysis. Among them, the most significant is the high disease activity [55, 56]. Another study evaluating the presence of invasive fungal infections in patients with connective tissue diseases mainly SLE found that underlying interstitial pneumonia was also a condition more likely to develop fungal infection [57]. Fei et al. [43] found that in a cohort of SLE patients the most prevalent infection site was the lung, accounting for over 60% of cases. The main causal pathogens were bacteria/fungus (mixed infections). *Pneumocystis jirovecii* is an opportunistic fungal pathogen that can cause severe infections, most commonly pneumonia in immunocompromised hosts such as SLE patients. In a meta-analysis of 2120 patients with SLE, approximately 5% developed pneumocystis pneumonia yet the mortality was 46% [58]. Prophylactic treatment for this infection is not accepted due to its low frequency and secondary events; hence it is necessary to keep in mind the possibility of developing this opportunistic infection [59]. Cryptococcal meningitis is one of the most important CNS infections in SLE patients, with an estimated prevalence of 0.5%. This infection may be misdiagnosed as psychosis triggered by steroid treatment, CNS lupus disease activity, or infection caused by non-fungal pathogens due to the nonstandard diagnostic strategy for cryptococcal meningitis. Therefore, a high suspicion and better prevention and management strategies against this type of infections are necessary [60].

A Practical Approach to Infections

Systemic lupus erythematosus by itself may predispose to infections; on the other hand treatment may also contribute to repeated infections in these patients, and therefore the use of immunosuppressant agents must be prescribed judiciously, especially glucocorticoids, employing them for the shortest period and at the lowest dose possible [61]. The distinction between lupus flare and infections may be difficult. Different tools have been employed to make that distinction, such as some biomarkers like anti-dsDNA antibodies, complement (C3 and C4), ESR, anti-C1q antibodies, and activity on urinary sediment, which are included in certain scales to measure disease activity. At the same time, possible biomarkers of infection in SLE patients include CRP and procalcitonine. The delta neutrophil index (DNI) is a new index calculated by subtracting the fraction of mature polymorphonuclear leucocytes from myeloperoxidase reactive cells which may be used as a marker of bacteremia or sepsis. A high DNI is better than CRP in correlating with severe sepsis or septic shock in critically ill patients and could be a marker for a prompt diagnosis and prognosis in an infected patient [62, 63]. Platelets are at the crossroads between the immune system, clotting cascade, and endothelial cells; therefore another clinical useful biomarker may be the platelet-neutrophil aggregates [64]. Other biomarkers have been proposed to differentiate SLE activity infections such as neutrophil-to-lymphocyte ratio plus C-reactive protein increases specificity by more than 90% compared to C-reactive protein alone [6]. Another recent study using genetic microarray technology identified seven genes expressed in patients with active SLE and one in patients with SLE and infection [5]. However none of these markers have enough power to confirm or rule out an infection. Hence, combining two or more tests has been suggested for a more accurate prediction of infection.

Another important aspect for prevention of infections in SLE is vaccination. Live vaccines should be avoided in SLE patients with active disease or on high-dose immunosuppressive therapy. Recommended vaccinations in adult SLE patients include influenza, pneumococcal, herpes zoster, human papillomavirus, and hepatitis B virus. Influenza vaccination (trivalent inactivated) every year is recommended for all SLE patients, except during disease flare. Other vaccinations required in SLE patients include tetanus toxoid in combination with diphtheria [65, 66].

Another type of prevention includes TLR antagonists, namely, quinine antimalarial drugs that reduce incidence of infections and mortality in lupus. SLE patients taking antimalarials are 16 times less likely to develop a major infection [67].

Antibiotic prophylaxis has been suggested in SLE patients with lymphopenia at risk for developing opportunistic infections, such as *Pneumocystis jirovecii*, indicated in patients with CD4+ T cell count less than 250/μl, total lymphocyte count less than 750/μl, interstitial pulmonary fibrosis, high disease activity, severe nephritis, or chronic use of prednisone more or equal to 20 mg/day. Prior to invasive dental procedures, antibiotic prophylaxis is also recommended to prevent bacterial endocarditis [67, 68].

Rare Infections in SLE: A Clinical Challenge

There is a group of rare infections in patients with SLE who are a real diagnostic and therapeutic challenge. These infections can exacerbate SLE, can mimic active SLE, and can occur anywhere in the world or be characteristic of a specific geographic region. Therefore all physicians must know their clinical manifestations in the context of a patient with SLE.

HIV Infection in a Patient with SLE

Up to 80 cases of SLE and HIV infection since 1988 have been described to date**.** HIV infection shares a series of clinical manifestations with SLE, such as fever, arthralgia, arthritis, myalgia, skin rash, lymphadenopathy, cytopenias, pulmonary, cardiovascular, renal, and CNS involvement. The patient with HIV can present autoantibodies and laboratory data, characteristics of SLE: ANA, anti-dsDNA, anti-Sm, anticardiolipin antibodies, leukopenia, lymphopenia, anemia, and thrombocytopenia. Hypocomplementemia has not been well documented in HIV infection; therefore it can help with the correct diagnosis. HIV infection can occur in a patient with a previous diagnosis of SLE, concomitant, or before the diagnosis of SLE. Therefore, in all patients with risk factors for HIV and clinical manifestations of SLE, the corresponding laboratory tests should be requested. Confirmatory HIV test is mandatory because false positives for HIV have been reported in SLE patients. These false positives occur by cross-reaction of autoantibodies with antigen characteristic of SLE and p18, p24 antigens from HIV. In relation to the treatment of SLE and HIV, it is important to consider that high doses of steroids, immunosuppressants, and biological therapy can increase viral load and reactivate HIV infection. However, the treatment for SLE can be indicated if CD4+ T cell count is above 200 cells/mm^3 and the HIV viral activity is completely suppressed. The description of cases of SLE after the era of highly active antiretroviral therapy (HAART) is striking. To explain this fact, it has been suggested that the emergence of SLE in HIV-infected individuals managed on HAART represents a unique type of immune reconstitution inflammatory syndrome (IRIS) [6, 69–73]. However, the mechanisms to explain the coexistence of SLE and HIV have not yet been fully clarified.

Strongyloides stercoralis and Systemic Lupus Erythematosus

Strongyloides stercoralis is an infection caused by an intestinal nematode and is distributed in all parts of the world. The massive invasion of the gastrointestinal tract and lungs occurs mainly in immunosuppressed hosts and the clinical picture is called hyperinfection syndrome, which has a high morbidity and mortality. The clinical picture of this syndrome is characterized by profound malabsorption, diarrhea, electrolyte imbalance, gram-negative or opportunistic fungal sepsis, coma, and death. The treatment of systemic infection due to *Strongyloides stercoralis* with either thiabendazole 25 mg/kg orally twice daily is satisfactory if the diagnosis is made early. However, in the immunocompromised host the treatment should be longer, with serial samples of stool and sputum until the nematode disappears [74, 75].

The frequency of *S. stercoralis* infection in SLE is 1.3%. The first case of SLE and hyperinfection syndrome by strongyloidiasis (SHS) was published in 1984 and since then, 18 cases have been published in different parts of the world, with a mortality rate of 27.7% (5/18). Practically all patients with SLE were highly active of SLE and they were being treated with high doses of steroids and immunosuppressants. The persistence of SLE activity and the development of fever, nausea, vomiting, diarrhea, cough, respiratory failure, and pulmonary hemorrhage should make one think of SHS [76–83].

Conclusions

Infection remains an important cause of mortality and morbidity in SLE patients. Infectious agents may precipitate disease flare and exacerbate autoimmunity, changing the natural history of disease and worsening outcomes in these patients. Therefore, there is an urgent need to implement improvements in early detection, treatment, and prevention in order to reduce the chance of infection in SLE patients.

There is a sub-registry of infections in SLE, especially in developing countries, and the risk factors for infections in SLE patients are not fully known. A recent study suggests high doses of steroids and high activity rates are the main predictors of infections in the first 2 years of evolution of SLE. Other studies indicate that prednisone over 7.5–10 mg/day, high-dose pulses of methylprednisolone, and high-dose regimens of cyclophosphamide are the main risk factors for infection. Bacterial infections are the most frequent infection in SLE patients. However, this pattern of infections in SLE can change according to the epidemiological and clinical conditions of each region or country [84, 85]. All these studies emphasize the need to investigate in each country the risk factors for the development of infections in SLE, in order to reduce the morbidity and mortality of our patients.

New biomarkers are needed to help differentiate with high sensitivity and specificity infections of relapses in patients with SLE. A recent study suggests that CD64 expression on neutrophils to diagnose bacterial infection was 85% and 84%, respectively, whereas the sensitivity and specificity of procalcitonin was 75% and 85%, respectively [86].

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Vaccines in Rheumatic Diseases

39

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Abbreviations

ACR	American College of Rheumatology
AIRD	Autoimmune inflammatory rheumatic diseases
Anti-HBs ab	Antibodies against the HBV surface antigens
BCG	Bacillus Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COMORA	Comorbidities in rheumatoid arthritis
CS	Corticosteroids
DMARDs	Disease-modifying anti-rheumatic drugs
DTaP	Diphtheria, tetanus, and pertussis vaccine
EULAR	European League Against Rheumatism
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IDSA	Infectious Diseases Society of America
IPD	Invasive pneumococcal disease
(MenACWY)	Polysaccharide and conjugate against serogroups A, C, W, and Y meningococcal vaccine
MenB	Recombinant vaccine against serogroup B of meningococcus
MMR	Measles, mumps, and rubella vaccine
MTX	Methotrexate
PCV13	13-Valent pneumococcal conjugate vaccine
PPV23	23-Valent polysaccharide vaccine
RA	Rheumatoid arthritis
RR	Relative risk
RZV	Recombinant zoster vaccine
SLE	Systemic lupus erythematous
SS	Systemic sclerosis
TB	Tuberculosis
Td	Tetanus/diphtheria
TNFi	Tumoral necrosis factor inhibitors
UK	United Kingdom
VZV	Varicella zoster virus
YEL-AND	Yellow fever vaccine-associated neurologic disease
YEL-AVD	Yellow fever vaccine-associated viscerotropic disease
ZVL	Zoster vaccine live

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Introduction

Vaccination is one of the most effective public health strategies to prevent infectious diseases because it reduces their severity and prevent complications thereof and also reduces the rate of morbidity and mortality in vulnerable groups such as children, the elderly, patients who use immunomodulatory medications, or patients with autoimmune inflammatory rheumatic diseases (AIRD).

Patients with AIRD have twice the risk of acquiring a confirmed infection as compared to the general population; there is also an increased number of hospitalization days to the severity of the infection [1, 2].

The cause of this increased susceptibility for infections is due to both the underlying immune dysfunction characteristics of each AIRD and to the use of immunomodulatory drugs [3].

There are four distinct types of vaccines: (1) live attenuated microorganisms, (2) inactivated microorganisms, (3) conjugated subunits (polysaccharides conjugated with proteins), and (4) toxoids (heat-inactivated toxins). All of these different vaccine types confer specific immunity by inducing antibody production and by generating immune cell memory. Live attenuated vaccines activate both innate and adaptive immunity as an active infection would do, rendering these

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_39

vaccines more effective as compared to inactivated vaccines, which contain complete organisms, subunits, or toxins that bear pathogen recognition patterns capable of inducing strong innate immune responses [4–6]. Of note is the vaccine that bears the bacillus Calmette-Guérin (BCG), which activates CD4 and CD8 T lymphocytes, resulting in strong local and systemic inflammatory reactions.

Despite the high effectiveness of the live attenuated microorganism vaccine type, these are contraindicated in immunosuppressed patients due to the risk of vaccine-induced disease from viral replication. However, this specific type of vaccine can be prescribed even to patients with AIRD who receive low levels of immunosuppressive therapy, defined as a dose of prednisone or the equivalent of <20 mg/d methotrexate <0.4 mg/kg/week, or azathioprine <3 mg/kg/d, according to the Infectious Diseases Society of America (IDSA) [7, 8].

Regarding inactivated vaccines, it is safe to prescribe these to patients with AIRD because they are not associated with a higher risk for inducing adverse effects or reactivation of the underlying pathology; they possess reduced immunogenicity depending on the pathology and immunosuppressive therapy (Table 39.1). Thus, it is recommended to follow the guidelines published for these patients [1].

Vaccination is also one of the most cost-effective and cost-saving tools to reduce the burden of infection in a population. Both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have published general recommendations for the application of vaccines in patients with AIRD (Table 39.2), which are under the vaccination scheme of immunosuppressed adults by the Centers for Disease Control and Prevention (CDC) [7, 9–11]. Another set of guidelines were developed for Latin-American patients [12] (Fig. 39.1).

This chapter focuses on the indications, contraindications, and efficacy of the vaccines included in the adult vaccination schedules of patients with AIRD and special considerations for patients traveling abroad.

Influenza Vaccine

Epidemiology

The incidence of influenza in patients with AIRD has not, to our knowledge, been established; however, it is known that the incidence is greater in patients with AIRD when compared to healthy subjects. This was confirmed in a retrospective cohort of patients with rheumatoid arthritis (RA), where the incidence of this viral infection was found to be higher (409.3 vs. 306.1 cases per 100,000 patient-years) [13]. Additionally, the increased rate of morbidity and mortality due to influenza infection in patients with RA is known; sometimes it is approximately double when compared with healthy subjects, with the subgroup of elderly patients with the highest risk: approximately 1.56 (95% confidence interval [CI], 1.23–2.02) for hospitalizations and 2.67 (95% CI, 2.26–3.16) for mortality, compared to subjects without this pathology [3].

Efficacy and Safety

There are different types of influenza vaccines available, including the inactivated trivalent or quadrivalent vaccine, the live attenuated virus vaccine, the recombinant vaccine, and a vaccine developed in cell culture. The majority of Latin-American countries utilize the inactivated influenza vaccine [12].

Regarding effectiveness of the vaccine, it is measured mainly through hemagglutination inhibition assay; in adults, a degree >40 units correlates with adequate protection; it is generally considered that >90% of healthy young adults will achieve this efficacy. The proportion decreases in elderly individuals and immunosuppressed patients. On the other hand, patients with AIRD exhibit lesser efficacy and a lower level of adequate seroprotection as compared to healthy subjects [3, 14, 15].

Table 39.1 Immune response following vaccination according to treatment

Vaccine	Low-dose corticosteroids	MTX	DMARDs	TNFi	Rituximab	Non- TNFi biologics
Influenza	✓	✓	✓	✓	↓↓	✓
Pneumococcal	✓	↓↓	↓↓	✓	↓↓	↓↓
Hepatitis B	✓	↓	↓	↓↓	?	?
Hepatitis A	✓	↓	✓	↓	?	?
Herpes zoster	✓	✓	✓	?	?	?
Human papillomavirus[a]	✓	✓	✓	?	?	?
Td	✓	✓	✓	✓	✓	✓

✓ adequate response, ↓ diminished response, ↓↓ very diminished response, ? there is no evidence, *MTX* methotrexate, *TNFi* tumor necrosis factor inhibitor, *Td* tetanus and diphtheria toxoids

[a]A decrease in immunogenicity has been observed in patients with SLE in treatment with mycophenolate mofetil plus low-dose corticosteroids (CS) [3, 7–13, 15]

Table 39.2 Recommendations for Vaccination

General recommendations
A general assessment should be made on all patients with AIRD to know their previous vaccination scheme
Ideally, *vaccines* should be administered 4 weeks prior to the start of immunomodulatory medications, especially before starting B cell depleting biological therapy, and preferably in patients with stable disease
Waiting to start treatment at least 2 weeks after inactivated vaccines
Booster vaccination may be required
Non-live vaccines can be safely administered. Live attenuate of vaccines should be avoided whenever possible in immunosuppressed patients with AIRD
Except for the hepatitis B vaccine, the measurement of antibody titers is not recommended.
Consider the revaccination of all vaccines received during immunomodulatory medications for at least 3 months after suspending immunosuppression
Specific recommendations
All patients must receive the anti-influenza vaccination annually
Pneumococcal vaccinations are recommended for all patients with the use of immunomodulatory medications
All patients with negative serology for hepatitis B should be vaccinated. The response to immunization should be measured 1–2 months after receiving the third dose, and revaccination is recommended in case of not having adequate titers
Vaccination for hepatitis A is recommended in patients who will travel to endemic areas. A 2-dose schedule is suggested 6 months prior to exposure
Anti-HPV vaccination is suggested for all young adults without previous vaccination scheme, with a 3-dose schedule
The anti-tetanus vaccine should be applied every 10 years. In case of presenting a contaminated wound in patients with rituximab use in the last 24 weeks, administration of tetanus immunoglobulin is also recommended
Patients with AIRD should receive the anti-VZV vaccine preferably before starting immunosuppressive therapy. In the case of patients receiving immunosuppressive treatment, this cannot be applied specifically in patients with biological treatment
In patients who are hyposplenic/asplenic with AIRD, vaccination by *Haemophilus influenzae* b and meningococcal is also recommended
The BCG vaccination is not recommended

AIRD autoimmune inflammatory rheumatic diseases, *HPV* human papillomavirus, *VZV* varicella zoster virus, *BCG* bacillus Calmette-Guérin [3, 7–13, 15]

Thirty percent of patients with RA will not achieve adequate protection, as is also true for other rheumatic diseases, except for patients with systemic lupus erythematous (SLE), in whom there are contradictory results: some studies show greater protective response in SLE patients compared to RA and a lower rate of influenza infections, while in other studies, these two diseases show similar results [14, 16–19].

It is interesting to know that the treatment with disease-modifying anti-rheumatic drugs (DMARDSs), corticosteroids (CS), tumoral necrosis factor inhibitors (TNFi), or other non-TNFi biologics do not profoundly impair the response of the vaccination, except in patients under rituximab therapy, in whom the effectiveness of the vaccine appears to be widely diminished. Thus, if there is a drop below 10% in peripheral B lymphocyte counts, booster is recommended [20–24].

The influenza vaccine is considered very safe and is employed worldwide in annual vaccination campaigns [12].

The incidence of adverse effects of the influenza vaccine in patients with AIRD is similar to those observed in healthy subjects, the main adverse effect being local reactions. A meta-analysis is noteworthy, which was carried out in patients with SLE, where there was no increased risk of adverse reactions in subjects with SLE compared to healthy subjects (relative risk (RR) 2.0, 95% CI 0.5–8.4, $p = 0.3$, heterogeneity $p < 0.001$, I2 = 81%) [16]. In addition to this, the available information demonstrates that the influenza vaccine does not affect disease activity in patients with SLE, including renal involvement, laboratory abnormalities, or requirement for increasing steroids or cytotoxic drugs. Although there are sporadic cases that show an increase in the titer of autoantibodies after influenza vaccination, this increment is transient and exerts no clinical effect [16, 18, 19, 25, 26].

Recommendations

1. Vaccination: The annual application of the anti-influenza vaccine is recommended in all patients with AIRD, regardless of their treatment. In the case of patients with rituximab use, it is suggested to apply the vaccination prior to the initiation of this humanized chimeric anti-CD20 monoclonal antibody or as long as possible after the administration of the biologic agent [7, 11, 15].
2. Booster: Booster influenza vaccination is not recommended, except for patients who did not previously receive the vaccine or those who were treated with rituximab, in whom a discrete benefit was observed [27, 28].
3. To provide increased protection to patients with AIRD patients against influenza, the vaccination of household contacts is also suggested [12].
4. Better programs are needed to expand vaccine coverage: Despite the existing recommendations for the administration of this vaccine, there is no adequate coverage of this vaccine worldwide; according to the COMORA (comorbidities in rheumatoid arthritis) study, a low coverage of only 25.3% (95% CI, 23.8–26.5) was reported [29]; in another recently published study from the United Kingdom (UK), the authors observed that, although vaccination rates were higher, only patients older than 65 years had adequate coverage. Therefore, there should be more educational programs to improve this situation [30].

Despite international recommendations for influenza vaccination, a low prevalence of this vaccination among RA patients, with huge disparity between countries, was observed.

Vaccine	19-21 years	22-26 years	27-49 years	50-64 years	>65 years
Influenza	1 dose annually				
PCV13	1 dose in unvaccinated patients				
PPV23	1 dose of PPSV23 at least 8 weeks after PCV13, and a second dose of PPSV23 at least 5 years after the first dose of PPSV23				
HepB	3 doses (0, 1 and 6 months) in unvaccinated patients with Risk Factors for HBV infection				
HepA	2 doses (0 and 6-12 months) in patients travelling to endemic areas				
RZV				2 doses (0 and 2-6 months)	
ZVL					1 dose (>60 years old)
HPV	3 doses (0, 1 and 6 months) in patients who started vaccination after age 15 2 doses (0 and 2-6 months) in patients who started before age 15				
MMR	1 dose (2 doses in patients with risk factors: students, health-care personnel and international travelers) CONTRAINDICATED IN PATIENTS RECEIVING IMMUNOSUPPRESSIVE THERAPY				
DTaP	1 dose in unvaccinated patients				
Td	Booster every 10 years				
MenACWY	2 doses should with a minimum interval of 8 week plus 1 dose every 5 years				
HiB	1 dose (3 monthly doses from 6-12 months post-HSCT				
YF	1 dose in unvaccinated patients CONTRAINDICATED IN PATIENTS RECEIVING IMMUNOSUPPRESSIVE THERAPY				

Specific cases All patients Contraindicated

Fig. 39.1 Adult immunization schedule adjusted for patients with AIRD. PCV13 13-valent pneumococcal conjugate vaccine, PPV23 23-valent polysaccharide vaccine, HepB hepatitis B vaccine, HBV, hepatitis B virus, HepA hepatitis A vaccine, RZV recombinant zoster vaccine, ZVL zoster vac- cine live, HPV human papillomavirus vaccine, MMR Measles, Mumps, and Rubella (MMR) vaccine DTaP tetanus/diphtheria/pertussis vaccine, Td diphtheria toxoid, MenACWY, polysaccharide vaccine conjugated with protein against serogroups A, C, W, and Y, Hib Haemophilus influenzae type b vaccine, HSCThemat opoieticstemcelltransplant,YF yellowfever [3, 7–13, 15, 26, 42, 45, 50, 52, 59, 61, 62, 64, 66]

Pneumococcal Vaccine

Epidemiology

Respiratory tract infections (RTI) are very common among patients with AIRD. *Streptococcus pneumoniae* is the main cause of bacterial community-acquired pneumonia; high-risk individuals are patients with diabetes, particularly those over 65 years of age; immunosuppressed patients, or patients with a chronic disease such as AIRD, are at higher risk of developing invasive pneumococcal disease (IPD, bacteremia, meningitis) or pneumonia, with a relative risk (RR) of 10.3 for IPD and of 8.2 for pneumonia (95% CI, 9.7–11.0 and 8.2–8.3, respectively). Specifically, in the case of patients with AIRD, it is known that they have an increased need for hospitalization due to secondary infections caused by this bacterium. The relative hazard (RH) for RA is 2.5 (95% CI, 2.4–2.5), the RH for systemic sclerosis [SS] is 4.2 (95% CI, 3.8–4.7), for Sjögren syndrome the RH is 3.2 (95% CI, 2.9–3.5), and for SLE RH is 5.0 (95% CI 4.6–5.4) [13, 31].

Efficacy and Safety

There are two types of vaccines: the 23-valent polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). In general, the polysaccharide vaccine is less immunogenic than PCV13, due to the fact that the latter is linked (conjugated) to a nontoxic protein such as the diphtheria toxin, which increases the immunogenicity of the vaccine and triggers an immunological memory [15, 32]. However, the advantage of PPV23 is that it offers a coverage of around 85–95%; thus, it is widely employed in adults [8].

In the case of the PPV23 vaccine, the antibody titers of two strains included in this formulation evaluate the response and protection, considering as an adequate response, an increase of at least twice the level of antibodies, and a protection antibody level of >1.3 mcg/ml [32].

With regard to the treatment, it was observed that immunosuppressive drugs decrease the effectiveness of PPV23. Two exceptions to this include low doses of CS and TNFi, which, in general, does not impair the development of the postvaccination protective antibody. On the other hand,

patients receiving doses of >10 mg/d of prednisone or the equivalent exhibited lower immune response rates that are maintained over time [32].

With respect to patients who use TNFi, it is considered that they have an adequate immune response although, in some studies, it was observed that patients treated with etanercept or infliximab, but not with certolizumab, have adequate responses to the vaccine [15, 33].

More recently, multiple studies showed that methotrexate (MTX) decreases the effectiveness of the vaccine in dose-dependent fashion, which is also true for other DMARDs, such as cyclophosphamide, mycophenolate mofetil, and azathioprine [15, 32, 34].

As for other immunomodulatory drugs, the results are variable; for instance, tacrolimus and tocilizumab exert no influence on the immune response after PPV23 vaccination whereas other drugs, such as abatacept and tofacitinib, show a slight decrease in the immune response, while rituximab therapy induces significant impairment in the development of the immune response both for PPV23 and for PCV13 [32, 35–38].

With respect to safety, both types of vaccines, PCV13 and PPV23, are well tolerated in subjects with AIRD. The most common adverse events for both vaccines include local reactions in up to 24% of patients for PPV23 and in up to 50% of patients for PCV13, and systemic symptoms such as malaise, fever, or irritability are observed in up to 85% of patients in both types of vaccine [2].

Booster

The prime-boost strategy combining the conjugated and unconjugated pneumococcal vaccines is recommended for immunocompromised patients; thus it is indicated in patients with AIRD, due to the poor immunogenicity associated with the majority of drug treatments. In several studies, an improvement in the immune response is observed after the prime-boost strategy was confirmed, which consists of the initial administration of the PCV13 vaccine plus one dose of PPSV23 at least 8 weeks after PCV13 and a second dose of PPSV23 at least 5 years after the first dose of PPSV23 [32].

Regarding the time of vaccine effectiveness, it was observed that a considerable proportion of patients who initially have adequate antibody titers maintained good responses for up to 10 years after the vaccine, regardless of immunosuppressive treatment or type of AIRD. Thus, measuring antibody titers prior to the application appears to be a better alternative rather than indicating application of the vaccine every 5 years [35].

Recommendations

1. Regardless of the underlying therapy or factors, such as age, on the response to pneumococcal vaccines in patients with RA or other rheumatic diseases, these vaccines should be administered to all patients with AIRD [12].
2. It is recommended to vaccinate patients prior to the start of immunosuppressive treatment [3, 7, 11].
3. In the case that patients are already on immunosuppressive therapy, consider the administration of PCV13 initially, followed by the administration of PPV23 8 weeks later [3, 7, 11, 32].
4. Apply PPV23 vaccine every 5 years [3, 7, 11].

Hepatitis B Vaccine

Epidemiology

The prevalence of hepatitis B virus (HBV) infection is approximately 3.6% (95% CI 3.6–3.6) worldwide, being higher in Africa (8.83%, 95% CI 8.82–8.83) and the Western Pacific region (5.26%, 95% CI 5.26–5.26) [39]. Classically, it is considered that patients with AIRD have an increased risk of reactivation of HBV infection, the latter reported in up to 8.6% in some studies. However, with highly effective treatment for this condition, this prevalence has decreased considerably to 0.014 (95% CI 0.013–0.016) [40].

Efficacy and Safety

There are different types of vaccines; however, all are recombinant vaccines, which are over 95% HBsAg protein and are interchangeable with each other. Vaccination is administered at months 0, 1, and 6; at 4–8 weeks after the application of the third dose, the antibody levels should be measured, including those of antibodies against the HBV surface antigens (Anti-HBs ab). If this is <10 mIU/ml, a fourth dose should be administered, and the levels should be measured again. If an inadequate response persists, screening should be performed again to detect HBV infection and, in the case of this being negative, two more monthly doses can be administered [8, 41, 42].

Vaccination against HBV in patients with negative screening has been questioned due to the increased risk of adverse effects and its low effectiveness in patients with immunosuppressive treatment. This latter appears to

depend on the type of vaccine used. In those studies in which the ENGERIX-B vaccine (20 microgram/liter Hep B vaccine) is used, adequate responses were reported in patients under DMARDs. Studies in which other vaccines have been used, such as HBVAXPRO-10 (10 microgram/liter Hep B vaccine), patients have presented a reduced response; therefore, the use of ENGERIX-B vaccine is strongly recommended [8, 41]. In some studies, a diminished immune response was observed in patients under TNFi therapy which has not, to our knowledge, been properly addressed [15, 34].

The most common adverse effects using this vaccine include headache, pain at the injection site, fever, and arthralgia, which last less than 48 h; however, there are reports of serious adverse effects immediately after the application of this vaccine: these include uveitis, nephrotic syndrome, Guillain-Barré syndrome, SLE flare-ups, and vasculitis [43, 44].

Booster

The duration of vaccine protection once immunosuppressive therapy has been initiated, to our knowledge, is unknown, although some studies report a decrease in antibody titers, particularly after TNFi, MTX, or rituximab therapy. However, the decrease is no less than 10 mIU/ml, therefore possessing no clinical relevance. Booster vaccination is not recommended [34].

Recommendations

1. Screening for HBV is recommended in all patients with AIRD prior to the start of immunosuppressive therapy [15].
2. It is suggested to vaccinate patients with AIRD in the case of their not having previous immunization and having risk factors for HBV infection (sex partners of HBsAg-positive persons; sexually active persons not in a long-term, mutually monogamous relationship; HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids; persons with end-stage renal disease; persons with diabetes mellitus; and persons with human immunodeficiency virus (HIV) infection) [8, 41, 42].
3. These persons should have three doses (at months 0, 1, and 6), and anti-HBs ab levels should be measured; if there is no titer of >10 mIU/ml, apply a fourth dose and rule out HBV infection again [8, 41, 42].
4. Booster vaccination is not recommended [34].

Hepatitis A Vaccine

Hepatitis A is a highly contagious viral disease that is spread across the globe; therefore, the hepatitis A vaccine is one of the most frequently used vaccines. The scheme includes the administration of two doses with an interval of 6–12 months. In immunosuppressed subjects after the first vaccination, low seroconversion rates are observed (10–62%), increasing considerably after the second dose (85–95%). However, patients with AIRD, with immunosuppressive therapy, especially with MTX, could have a much lower response. Thus, two additional vaccination schemes have been developed: one in which the administration of double doses is followed by a third dose at 6 months and a second scheme in which the three doses are administered at 0, 1, and 6 months. Both schemes have seroconversion rates similar to those observed in healthy controls; thus, they may represent a good alternative in these types of patients. This vaccine should be administered to patients with AIRD who are seronegative for hepatitis A. Regarding adverse reactions; these are minor and include local pain, headache, and malaise [45–48].

Recommendations

1. Consider vaccination for hepatitis A in patients traveling to endemic areas.
2. The vaccination schedule includes two doses administered within a difference of 6–12 months; however, in unvaccinated postexposure patients, it is recommended to administer a single dose plus the application of immunoglobulin [45].

Herpes Zoster Vaccine

Epidemiology

Herpes zoster infection is due to the latent reactivation of the varicella zoster virus (VZV). It occurs mainly in elderly, diabetic, and immunosuppressed patients, with an annual incidence of approximately 1% of all adults over 60 years of age. Patients with AIRD comprise a highly vulnerable group, although these changes are according to geographical regions, being higher in Asian patients, with an incidence of approximately 7.7 cases per 100 patient-years compared with 2.7 cases per 100 patient-years observed in Western Europe [2, 13, 34].

Recognized risk factors include age, female sex, and the use of corticosteroids (CS), biologics, and tofacitinib [12].

Regarding the type of AIRD, it was observed that patients with SLE or vasculitis, especially those treated with cyclophosphamide, are those entertaining the highest risk, which is 20 times higher than that observed in the general population [2, 49].

In the case of patients with RA, they have twice the risk as the general population, regardless of the immunosuppressive treatment, with the exception of CS, in which the risk moves in a dose-dependent manner; although some studies show similar risk numbers for all biological DMARDs, other reports demonstrate that the risk changes depending on the drug that was used, ranged from 4.7 cases per 100 patient-years with etanercept to 7.6 cases per 100 patient-years with tofacitinib [2, 34].

Efficacy and Safety

Previously, there was only one type of vaccine (ZVL, zoster vaccine live), which was essentially a larger-than-normal dose of the chickenpox vaccine, which contains the Oka strain of live attenuated VZV, with a reduction in reactivation of approximately 61.1% of cases and 66.5% of postherpetic neuralgia. However, its effectiveness decreased to approximately 55% in subjects aged over 70 years [2, 49].

Regarding the safety of this vaccine, it has been classically considered that immunosuppressed patients have an increased risk of presenting varicella secondary to the administration of the vaccine. For this reason, the CDC determined that its administration is safe only in patients receiving treatment with MTX (<0.4 mg/kg/week), azathioprine, low-to-moderate doses of systemic CS, or local CS injections. However, there are many observational studies in which the safety of this vaccine was evaluated in patients with DMARDs and biological drugs, in whom, although there is less effectiveness of the vaccine in patients with TNFi, rituximab, or high doses of CS or DMARDs, an increased risk of varicella incidence postvaccination was not observed. Therefore, in the 2015 American College of Rheumatology (ACR) Guidelines [7], vaccination is recommended for all patients aged >50 years, despite the increased risk of presenting the classically described varicella postvaccination [2, 8, 9, 13, 34].

Recently, a new vaccine (RZV, recombinant zoster vaccine) has come on the market. This is a subunit vaccine that contains a glycoprotein on the surface of the virus (glycoprotein E); this vaccine has an effectiveness of approximately 97.2%, with an effectiveness >89% in patients older than 70 years of age. In addition to this, the only adverse effects reported are myalgias, arthralgias, and fevers, which are self-limiting during a period not greater than 7 days after administration of the vaccine. Despite the advantages of this vaccine, to our knowledge it is still not yet available in all countries and there are still no data on its effectiveness in patients with AIRD and different types of immunomodulatory drugs [49, 50].

Recommendations

1. It is recommended to administer the herpes zoster vaccine to all patients >50 years of age, preferably prior to the start of immunosuppressive therapy, or to those receiving treatment with MTX (<0.4 mg/kg/week), azathioprine, low-to-moderate doses of systemic CS, or local injections of CS (intra-articular, in bursae or tendons) [2, 8, 9, 13, 34].
2. The administration of the RZV is preferred over the ZVL [49, 50].
3. In the case of patients with biological treatment, administer the vaccine preferably 1 month prior to the start of treatment or 1 month after discontinuing treatment [2, 8, 9, 13, 34].

Human Papillomavirus Vaccine

Epidemiology

Human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases worldwide. Serotypes 16 and 18 are associated with malignant cervical neoplasms, while serotypes 6 and 11 are associated to genital warts or condylomata. It is known that patients with AIRDs, especially those patients with SLE and RA, have an increased risk of developing this type of viral infection because of their diseases and the immunosuppressive drugs they receive and have up to 50% greater risk of presenting some high-grade cervical dysplasia and cervical cancer [15, 34, 51].

Efficacy and Safety

There are three types of vaccines, all of them are inactivated virus-like particles, a bivalent vaccine (genotypes 16 and 18) approved only for women, a quadrivalent vaccine (genotypes 6, 11, 16, and 18), and nine-valent vaccine that covers the same genotypes as the tetravalent plus genotypes 31, 33, 45, 52, and 58 [52].

The quadrivalent vaccine reduces HPV infections by approximately 90%, low-grade dysplasia by 45%, and high-grade dysplasia by 85% in women vaccinated before

age 26. There are studies in healthy women between 27 and 54 years of age in which this vaccine has been tested and found an efficacy >80% higher in women without HPV infection, with a reduction of cervical dysplasia of type cervical intraepithelial neoplasia grade 2 in these patients. However, when all patients are analyzed without selecting them according to their HPV DNA status, no benefit has been found, so it is not a cost-beneficial strategy and vaccination is not currently recommended in these patients [52–55].

In patients with AIRD, although evidence is limited, there appears to be a lower rate of seroconversion in patients with SLE compared with healthy subjects, especially in patients who receive mycophenolate mofetil and a low dose of CS [51–53, 56].

There are, to our knowledge, no data on the immunogenicity of this vaccine in patients with AIRD of the nine-valent vaccine. However, clinical trials in healthy subjects demonstrate non-inferiority when compared with the quadrivalent vaccine and superiority for the remaining genotypes. Therefore, if the vaccine is available, administration of the latter is strongly recommended.

With respect to the safety of these vaccines, there are some reports of cases in which the use of these vaccines has been linked to the development of SLE, Behçet disease, Raynaud disease, fibromyalgia, and type 1 diabetes; notwithstanding this, causality is not supported because the correlation is weak due to inadequate temporary associations. Thus, current data does not present enough evidence to associate the administration of this vaccine with the development of an autoimmune disease [51, 52, 57].

Independent investigators have described the onset of a chronic painful dysautonomic syndrome soon after HPV vaccination. The veracity of this syndrome is hotly debated. Many of the reported post-HPV vaccination cases fulfill fibromyalgia diagnostic criteria [58].

In the same manner, adverse neurological and venous thromboembolic events were also not strongly associated with vaccine usage [51, 52, 57].

Recommendations

1. Vaccinate all those patients under the age of 26 years [52, 56].
2. Although the vaccine is effective, there is not sufficient evidence to recommend vaccination in women over 26 years of age. Do not administer the vaccine to men older than 26 years of age [53–55].
3. Apply three doses (at 0, 1, and 6 months) if vaccination was initiated after 15 years of age or two doses (at 0 and 2–6 months) in patients who started vaccination prior to the age of 15 years [52, 56, 59].
4. Patients with incomplete scheme will only need to complete the scheme [52, 56].
5. Administer the quadrivalent or nine-valent vaccine to male patients. The administration of quadrivalent or nine-valent vaccines is preferred in female patients; however, it is also possible to administer the bivalent vaccine [60].

Other Vaccines

Measles, Mumps, and Rubella (MMR) Vaccine

MMR vaccine is a live attenuated type of vaccine. It is indicated in children older than 1 year of age, adults who did not receive this vaccine during childhood, subjects with negative serology for at least one of the three viruses and with risk factors for acquiring this infection (students, health personnel, international travelers), and adults who received a measles vaccine of an unknown type, an inactivated measles vaccine, or further attenuated measles vaccines accompanied by immunoglobulin. In addition, boosters are recommended for patients born after 1957. The vaccination schedule is one dose for the population in general and two doses for individuals with risk factors, with a minimal interval of 28 days between each vaccine, providing protection for life [61].

Adverse effects to this vaccine include immune thrombocytopenia, chronic arthritis (especially in young women and patients with psoriasis), transverse myelitis, and inflammatory bowel disease [43, 61].

Because it is a live attenuated virus vaccine, it is contraindicated in patients receiving immunosuppressive medications or moderate-to-high-dose CS therapy [8, 43, 61].

Bacillus Calmette-Guérin Vaccine

Although tuberculosis (TB) is highly prevalent in some countries, the BCG vaccine has not shown to be effective for the prevention of TB in adults. The vaccine does not protect individuals who are already infected with TB. Thus, the application of this vaccine is only in children at high risk and in exposed adults, including health personnel, especially patients with resistant strains of TB. In addition to this, the use of BCG in patients with urothelial carcinoma as part of the treatment of this pathology has been associated with the appearance of rheumatic diseases such as RA, spondyloarthropathies, and dermatomyositis. For these reasons, the BCG vaccination is not recommended for patients with AIRD. It is, however, recommended prior to the initiation of TNFi to perform TB screening and in the case of latent TB that required chemoprophylaxis [1, 3, 43].

Diphtheria, Tetanus, and Pertussis Vaccine

There are two main types of vaccines against these diseases: the tetanus/diphtheria/pertussis (DTaP) vaccine and the tetanus/diphtheria (Td) vaccine. The DTaP consists of pertussis antigens and diphtheria and tetanus toxoids; diphtheria tetanus toxoids differ depending on the type and amount of pertussis antigen. Both vaccines are effective in patients with RA and in patients with SLE, although in the latter, the effectiveness of the vaccine can be affected by the disease activity. In general, immunosuppressive treatment does not affect the effectiveness of these vaccines, except for rituximab if it is administered less than 24 weeks prior to vaccination [12, 50, 62].

The recommendations for these vaccines are the same as for the general population: one dose of DTaP vaccine should be administered to adults who have not previously received it, followed by 12 doses of Td booster every 10 years [12, 50, 62].

Meningococcal Vaccine

There are two meningococcal vaccines: the polysaccharide vaccine conjugated with protein against serogroups A, C, W, and Y (MenACWY) and the recombinant vaccine against serogroup B (MenB), although the latter is only used in children and adolescents <16 years, without factors of risk for meningococcal infection. The MenACWY vaccine possesses adequate efficacy in patients with AIRD, the latter not diminished despite immunosuppressive treatment, including TNFi and other biologics. The indications for these vaccines are the same as in the general population; that is, they should be administered in adults with complement deficiency and anatomic or functional hypo-/asplenia, patients traveling to sub-Saharan Africa or to Mecca, patients receiving treatment with eculizumab, and patients with HIV. The type of vaccine administered depends on the epidemiology of the meningococcal diseases and the serogroup distribution in each country [12]. Two doses should be administered with a minimal interval of 8 weeks, followed by one dose every 5 years [34, 63].

Haemophilus influenzae Type B Vaccine

Prior to the introduction of this vaccine in the current vaccination schedules, *Haemophilus influenzae* type b infection (Hib) was the leading cause of bacterial meningitis and a common cause of other invasive diseases (epiglottitis, pneumonia, septic arthritis, cellulitis, purulent pericarditis, and bacteremia) among children aged <5 years. The Hib vaccine is a conjugate vaccine, and it has an approximate effectiveness of 95%. In patients with AIRD, an effectiveness of 88% was seen. This vaccine is indicated in patients with HIV infection, anatomical or functional hypo-/asplenia, complement deficiency, hematopoietic stem cell transplants, and patients who received chemo- or radiotherapy [13, 64].

Yellow Fever Vaccine

Yellow fever is a disease with high endemic mortality in tropical areas of South America and sub-Saharan Africa. Because there is no effective treatment for this disease and in that it is accompanied by high mortality rates, vaccination is one of the most important measures to reduce its incidence. There are multiple vaccines available on the market; however, all are live attenuated viral vaccines, all with a good effectiveness (>94%); to our knowledge, there are no studies that evaluate the effectiveness of this vaccine in patients with AIRD. Adverse events of this vaccine include fever, headache, and myalgia, which are self-limiting in 5 days (10–30%), hypersensitivity, and, in very rare cases, two syndromes: yellow fever vaccine-associated neurologic disease (YEL-AND) and yellow fever vaccine-associated viscerotropic disease (YEL-AVD); YEL-AND represents a conglomerate of clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and, rarely, cranial nerve palsies, with an approximate incidence of 0.8 per 100,000 doses administered. YEL-AVD is a serious disease similar to yellow fever that is caused by the proliferation of the virus in multiple organs, leading the patient to multiple organ failure and death. It can occur within the first 18 days of administration of the vaccine, and it has an incidence of 0.3 cases per 100,000 doses of vaccine administered and a mortality of nearly 50%. Patients with autoimmune diseases have an increased risk of presenting YEL-AVD. In endemic countries, subjects are usually vaccinated in childhood. The Centers for Disease Control (CDC) recommends the administration of one dose of this vaccine to all unvaccinated patients traveling to endemic areas. A booster is indicated in subjects with HIV infection every 10 years. The administration of this vaccine in patients with AIRD and immunosuppressive treatment is contraindicated [12, 65, 66].

Argentine Hemorrhagic Fever Vaccine

Argentine hemorrhagic fever is an endemic disease in central Argentina, caused by the Junin virus and transmitted by the rodent *Calomys musculinus*. It has an approximate mortality of 30%. The vaccine against this pathology is an inactivated live virus vaccine and this has an efficiency of 95%. Indications include one dose in subjects older than 15 years

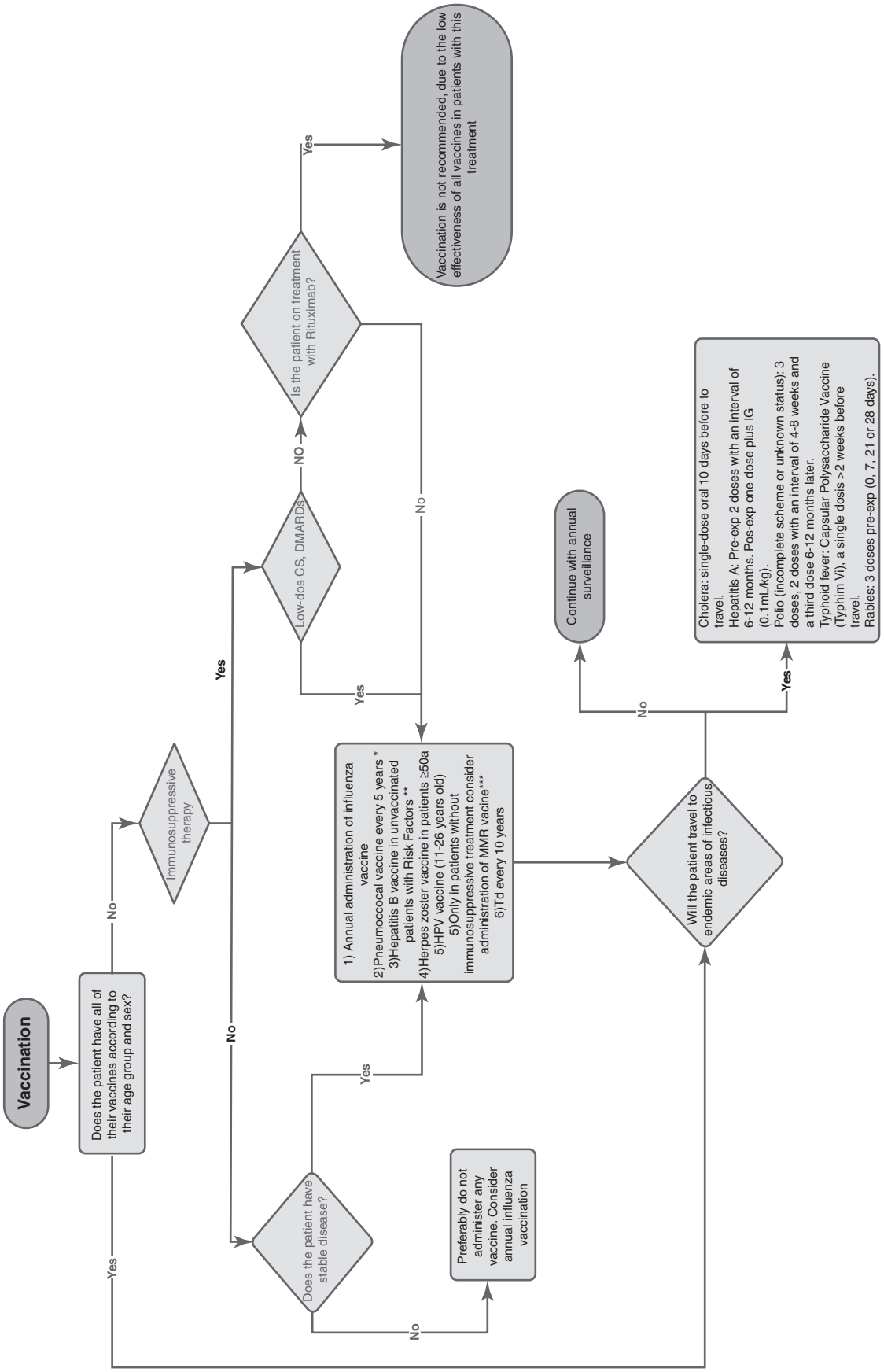

Fig. 39.2 Vaccination in patients with AIRD. *Consider that the effectiveness of pneumococcal vaccine decreases in patients treated with DMARDs, including MTX and non-anti-TNF biologics, especially with rituximab. **The effectiveness of the vaccine decreases in patients with TNFi. ***Adults without the vaccine or born after 1956 [3, 7–13, 15, 26, 42, 45, 50, 52, 59, 61, 62, 64, 66]

of age who live or work in endemic areas. There is, to our knowledge, no information about the vaccine's effectiveness and safety in patients with AIRD [12, 67].

Vaccination for Travelers with AIRDs

In the case of patients with AIRD who are going to travel, it is recommended that they have their complete vaccination scheme, and additional vaccines will be administered, which will vary depending on the place these patients will visit. Among the main vaccines for travelers are the vaccine against rabies in the case of the risk of animal bites and vaccines against hepatitis A, cholera, polio, yellow fever, Argentine hemorrhagic fever, and typhoid fever in case of travel to endemic areas. The doses of these vaccines are summarized in Fig. 39.2 [66].

Future Perspectives

Currently, there are multiple vaccines in development for different pathologies. One of these is the HIV vaccine. After the results published by the RV1447 trial in which a protection of 31.2% was observed, clinical trials were developed that are providing proof of the concept that vaccines that cause the production of antibodies do not neutralize the effector functions directed against the Env protein, which could provide adequate protection [68].

Another vaccine that is under development with promising results is the vaccine against Ebola virus disease. Although there are more than 36 registered clinical trials, only the results of the recombinant, vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Zaire ebolavirus (rVSV-ZEBOV) have been published. This appears to have an efficacy of around 94% with a duration of 24 months, although this vaccine is not yet approved; however, due to its promising results, its application has begun in some areas of Africa [69].

With respect to the dengue vaccine, one of the most promising approaches involves the creation of two flavivirus chimeric vaccines: dengue and yellow fever. The first tetravalent recombinant chimeric vaccine was released in 2015, with an effectiveness of around 60%; however, after its commercialization, there were reports of severe dengue in vaccinated individuals. Therefore, in September 2018, the World Health Organization (WHO) updated its recommendations, suggesting vaccination only in subjects who have already had dengue; thus, other potential vaccines are under clinical development against this pathology [70]. Finally, in line the previous example, clinical trials are currently carried out with animal models, in which an attempt is made to test the immunogenicity and safety of chimeric viruses of yellow fever and Zika virus. If good results were obtained for the latter, it would likely be a good candidate for the vaccine against the Zika virus [71, 72].

More recently, research is being developed that involves inactivated vaccines to prevent lethal fungal infections, particularly in patients with AIRD, in whom molecules were found that, in the future, can be targeted to improve vaccination efficacy by stimulating CD8+ T cells regarding the CD4+ T cell deficiency in these patients [73].

Conclusion

Patients with AIRD have an increased susceptibility to infectious diseases, many of which can be prevented through vaccination. On the other hand, the effectiveness of certain vaccines can be affected depending on the treatment; thus, the ideal time for the administration of these vaccines will always be prior to the initiation of immunomodulatory treatment. Except for some live attenuated virus vaccines, vaccination is safe in these patients despite their immunosuppression status. Therefore, it is necessary to improve coverage/protection in these patients and thus be able to be able to reduce the incidence, prevalence, morbidity, and mortality of infectious diseases effectively in this vulnerable population.

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Climate Change: Impact on Infectious Diseases

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Judd Shellito

Introduction

Climate change, through effects on both infectious pathogens and their hosts, is likely to alter the epidemiology and severity of human infectious diseases. In this chapter, we will address the difference between weather and climate and examine mechanistic pathways through which changes in climate may influence the expression of infectious diseases in humans. Finally, we will consider how climate change is predicted to affect specific infections.

Defining Our Terms: Weather Versus Climate

We are all familiar with weather. Weather is the state of the atmosphere with respect to temperature, humidity, precipitation, wind, and cloud cover. Short-term changes in weather are found in weather forecasts for the week or the weekend. Climate on the other hand is an average condition of weather over a long time, 20–30 years up to millions of years. Climate change is how these atmospheric conditions have changed or are predicted to change over that long time interval.

Climate change is often represented as changes in surface temperature of the earth (global warming) or as rising sea levels. For example, the average surface temperature of the earth has increased by 0.6 °C since the 1950s and sea level has increased by 10–20 cm over the same period [1]. While these changes may seem small at first glance, the cumulative effect of climate change over time is significant with an increase in atmospheric carbon dioxide, higher maximum and minimum temperature days, more heat waves and droughts, along with increased frequency and intensity of tropical storms and hurricanes. Rainfall patterns are changed, and there are more extremes of weather including floods, storms, and wildfires. Climate change is predicted to accelerate during the present century with an increase in average temperature of 1.4–5.8 °C by the end of the century and a corresponding rise in seal level [1, 2]. These changes have been summarized for the United States in a recent report [3]. The effects of these atmospheric changes on the ecology of living organisms are likely to be dramatic.

Climate change has been observed over many millions of years. The cause of these changes is unclear. However, much of the climate observed over the last and predicted for the coming century can be attributed to human activity. As human populations have increased, the need for energy production has also increased. Much of this energy production has been and continues to be met by burning of fossil fuels that emit carbon dioxide and other greenhouse gases. Deforestation and burning of biomass also releases carbon dioxide into the atmosphere. These gases trap heat within the atmosphere, preventing it from reflecting into space with resultant elevations of surface temperature [4]. This increase in surface temperature is further amplified by changes in vegetation and melting of surface ice leading to sea level rise [5].

Pathways Between Climate Change and Infectious Diseases

There are three pathways through which climate change is predicted to change the types and severity of infectious diseases affecting humans (Fig. 40.1):

1. Effect of climate change on the pathogen
2. Effect of climate change on disease vectors
3. Effect of climate change on the host

Changes in weather can influence infectious pathogens directly, mainly by altering the environment in which they grow. This could lead to increased human exposure as climate

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_40

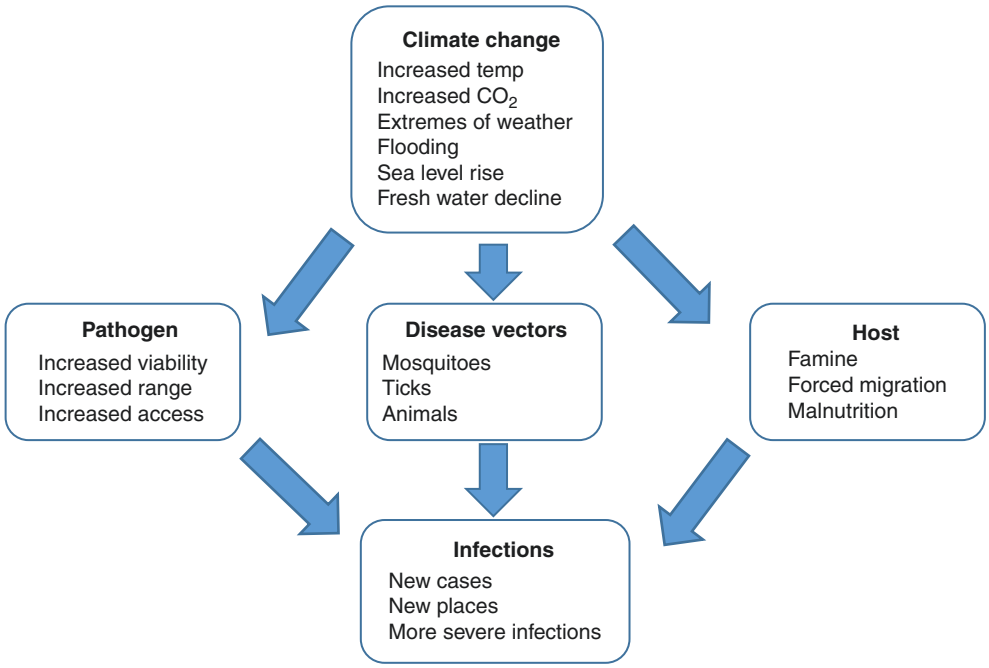

Fig. 40.1 Pathways between climate change and infectious diseases

change extends the range of a pathogen or increased transmission of infection from the environment as environmental changes favor dissemination to humans. Pathogens most likely to be affected by climate change are those pathogens that spend part of their life cycle outside the human host, in the soil or water, or in intermediate animal species. Also most likely to be affected are those pathogens that have a seasonal epidemiology, such as influenza, because these seasons will be altered though climate change. Climate change will impact food production systems and water purification leading more food-/waterborne infections.

Changes in weather are also likely to influence infectious diseases transmitted through an insect vector, such as malaria. Rising temperatures and changes in groundwater will affect the ecology of the insect vector. This may extend or restrict the ranges of the insect vectors with a corresponding effect on transmissible infection. Infectious diseases transmitted through an animal species will also be influenced by climate change. Change in temperature, sea level, and groundwater will influence the behavior and migration patterns of animals, leading to changes in infectious diseases transmitted through those animals. For example, outbreaks of human infections with Ebola virus have been linked to deforestation and climate change-induced stress on the habitats of fruit bats, a natural reservoir of the virus [6].

Finally, changes in weather can affect the human host leading to increased susceptibility to and/or increased virulence of an infectious disease. How could this occur? Climate change is predicted to cause dramatic changes in availability of human food sources whether they are plants or animals. These changes will be mediated through rising temperatures, changes in water availability for livestock or irrigation, and rising sea levels limiting coastal-based agriculture and aquaculture. It is likely then that coming years will see more areas with limited food availability and malnutrition. The effects of malnutrition on the immune system will translate into increased human infections. Also as food becomes scarce, human populations will have to travel to areas with more abundant food sources possibly bringing humans into contact with new pathogens or to increased human to human transmission of infection during forced migrations.

Effect of Climate Change on Specific Infections

Soil-Based Pathogens

Coccidioidomycosis is a human infection caused by *Coccidioides immitis*, a soil-based fungus. The hallmark infection is fungal pneumonia (valley fever) which follows inhalation of organisms (conidia) that have gone through a life cycle change in the soil. The disease has long been recognized to be confined to a particular geographic zone, where coccidioides organisms are resident in the soil. This endemic zone (the Lower Sonoran Life Zone) is found in parts of the southwestern United States and in northern Mexico. The ecology of the organism follows a "grow and blow" pattern in which a dry season is followed by a wet season followed by soil disturbance (wind, excavation). Airborne conidia can then be spread to other areas and potentially to humans. This "grow and blow" ecology defines the

geography of soil-based coccidioides and is already being altered by climate change. It should be noted that coccidioidomycosis is not transmissible from human to human; human infection requires contact with fungal organisms that have passed through the soil. Mean temperatures are rising in the Southwestern US along with increased case numbers of fungal pneumonia in the endemic zone [7]. Most importantly, changing climactic conditions have already resulted in soil residence and cases of valley fever in locations outside the typical endemic zone [8]. Clinicians are warned to be alert for cases coccidioidomycosis in locations where this infection has not been seen previously.

Histoplasmosis is another fungal infection endemic to the United States. It is a particular problem for immunosuppressed patients. The pathogen, *Histoplasma capsulatum*, is found in soil throughout the Ohio and Mississippi river valleys. Recent evidence suggests that the endemic range for histoplasma now extends into the Missouri River basin region – which includes Montana, North Dakota, South Dakota, and parts of Nebraska, Iowa, Kansas, and Missouri [9]. These areas have seen hotter and wetter averages over the past 50 years along with land use changes. It is anticipated that the range for this fungal pathogen will further extend with advancing climate change.

Parasitic Diseases – Malaria

Malaria is a parasitic disease which is spread through the bite of infected *Anopheles* mosquitos. Malaria caused 445,000 deaths worldwide in 2017 [10]. The disease is found mainly in tropical regions and human infection closely follows the geography of the mosquito vector. Climate change, particularly increased temperature, speeds up the life cycle of the *Anopheles* mosquito and enhances survival of both the insect and the malaria parasite within it. Climate change has already resulted in the spread of malaria into previously unaffected areas. Beginning in the 1950s, coincident with warmer and wetter weather, malaria spread in the highlands regions of East Africa with high morbidity and mortality [11]. Transmission of malaria and spread of the mosquito vector has been shown to be dependent on both temperature and rainfall [12]. It is likely that regions of the world with endemic malaria will show a northward shift of the malaria epidemic belt over central-northern Europe, Russia, northern Asia, and northern America [13]. Rogers and Randolph predicted that by 2050, falciparum malaria would add 23 million new human cases in previous uninfected locations but would also lose 25 million cases from current endemic areas no longer suitable for transmission [14]. The net result may be no change in total number of cases, but a change in the geographic range in which malaria occurs.

Viral Pathogens

Influenza viruses (A, B, and C) cause seasonal outbreaks of human infection worldwide. Influenza virus can infect pigs, birds, and humans. Outbreaks of infection occur in winter months in the Northern and Southern hemisphere, but can be seen throughout the year in the tropics. Influenza virus has a high mutation rate resulting in changes in the antigenic makeup of the viral coat. These mutations are monitored yearly in Asian bird populations to guide vaccine development for the coming year. A significant antigenic change (antigenic shift) can result in a widespread outbreak or pandemic. Pandemic influenza has been associated with high morbidity and mortality in 1918, 1957, 1968, 1977, and 2009. As a seasonal pathogen with a reservoir in birds, influenza is certain to be impacted by climate change through effects on the virus itself or the ecology of its animal hosts. Epidemiologic studies have shown the warm winters tend to be followed by more severe and earlier cases of influenza the following season [15]. Climate change is marked by increases in atmospheric carbon dioxide. Increasing carbon dioxide is matched by increased cases of influenza from 2003 to 2015, although a direct cause and effect relationship is unlikely [16]. Morbidity and mortality from influenza outbreaks in France have also been linked to the El Niño oscillation, a marker of climate change [17]. On the other hand, warmer weather may lead to less human to human transmission of influenza as people spend less time indoors and in close contact [18].

The influence of climactic conditions on viral infections is complex, with some infections predicted to increase and others to decrease in humans. Infections with respiratory syncytial virus (RSV) are likely to show a decrease with advancing climate change. RSV causes seasonal outbreaks of bronchiolitis in children beginning each year in autumn and ending in the spring. An analysis of RSV cases in England from 1981 to 2004 found that as the mean daily temperature increased by 0.5 °C per year, the number of emergency room RSV cases significantly decreased and the RSV season ended earlier [19]. This suggests a potential benefit of global warming for this particular pathogen.

Outbreaks of tropical hemorrhagic fever (dengue, Ebola) occur periodically, mainly in the tropics, and are a source of great concern due the highly contagious nature of these infections and the high mortality rate. Dengue is transmitted by the *Aedes aegypti* mosquito. There are 284 to 528 million cases of dengue infection each year [20]. Warmer temperatures increase the transmission potential of infected mosquitoes [21]. Statistical models predict an expanding range of dengue-infected mosquitoes with increased potential for human infection [22]. Ebola virus on the other hand is not believed to be transmitted by mosquitoes, but is resident in fruit bats with secondary transmission to monkeys and humans.

First recognized in humans in 1976, Ebola infection has occurred in periodic outbreaks in Africa with documented transmission worldwide. The most recent outbreak was in 2014 when the mortality rate was 90% [23]. Little is known about the potential effects of climate change on Ebola infections. Studies of fruit bats, the natural host of Ebola virus, have correlated desertification, deforestation, and rising temperatures with increased migration of fruit bats in search of food [24]. This migration has brought fruit bats into areas of Ebola outbreaks in humans. It is also likely that famine and forced migration of humans induced by climate change will contribute to transmission of Ebola and the likelihood of future outbreaks.

As seasonal infections, the viral encephalitides are likely to be profoundly affected by climate change. Central nervous system infections caused by the arboviruses include Japanese B encephalitis, St. Louis encephalitis virus, West Nile encephalitis virus, and Eastern, Western, and Venezuelan equine encephalitis virus. These infections are transmitted by mosquitoes so that climate changes that alter to range of the mosquito will influence the epidemiology of human infections. These changes may increase or decrease mosquito growth and spread, so it is difficult to predict how these infections will change over time within a geographic region. For example, drought has been shown to be more important than temperature as a factor increasing epidemics of West Nile encephalitis [25]. Tick-borne viral encephalitis occurs mainly in Russia, Scandinavia, and India. The range of the tick transmitting the disease is predicted to spread northward with increasing surface temperatures [26]. The Zika virus is a rapidly spreading arbovirus that causes devastating congenital brain defects in children. It has been postulated that El Niño conditions (warm temperatures followed by drought) lead to the explosive spread of Zika in Brazil in 2015 [27]. Spread of Zika is further amplified by international travel of asymptomatic (but viremic) travelers [28].

Bacterial Pathogens

In temperate regions, bacterial pneumonia tends to occur in the winter months [29]. With this in mind, climate change and global warming could decrease the incidence of bacterial pneumonia.

However, bacterial pneumonia also tracks influenza, so that changes in the epidemiology of influenza (as discussed above) will also influence bacterial pneumonia. On the other hand, in the tropics bacterial pneumonia tends to occur in the rainy season, probably due to increased crowding, exposure to biomass fuel, and decreased exposure to sunlight [30]. The Intergovernmental Panel on Climate Change predicts increased rainfall in tropical regions (Africa, Asia, Pacific, and South America) [31], which may be expected to correlate with increased cases of childhood pneumonia.

Cholera is a diarrheal disease caused by the bacterial pathogen, *Vibrio cholerae*. Cholera affects 3 million persons yearly with approximately 100,000 deaths [32]. The pathogen has a reservoir in local aquatic bodies (rivers, wetlands) where the bacteria attach to zooplankton [33]. Changes in surface temperatures and rainfall are predicted to cause increased outbreaks of cholera in coastal communities [34]. Climate change-induced pressures on water availability and purification may also contribute to cholera outbreaks. Other waterborne pathogens, such as cryptosporidium and norovirus, are also climate sensitive [35].

Spirochetal Pathogens

Lyme disease is a spirochetal infection caused by the tick *Borrelia burgdorferi* in the United States. The pathogen is transmitted by the bite of infected ticks. The disease is the most common tick-borne disease in the USA and Europe. The disease has a distinct regional prevalence with the majority of US cases occurring in the Northeast and Upper Midwest states. Climate change, as it impacts the life cycle and range of the deer tick, is predicted to influence the geographic range of Lyme disease. Cases of Lyme diseases are observed in heavily forested areas with peak incidence in the summer months. Both tick activity and survival depend on temperature and humidity. Predicted increases in average temperature with climate change are estimated to increase the number of cases of Lyme disease in the USA by 20% over the next 30 years [36]. The influence of climate change on the tick vector and on animal hosts are predicted to expand the range of disease northward into Canada and into the Midwest with a decline in southern states [37]. This means that physicians will start to see Lyme disease and its complications in places where it has not been previously encountered.

Leptospirosis is a zoonosis caused by spirochetes of the genus, *Leptospira*. The organism infects a wide variety of wild and domestic animals. Humans become infected with exposure to water or soil contaminated with animal urine or from infected animal tissues. Climate changes affecting animal habitats or water reservoirs will likely influence the prevalence and spread of leptospirosis in humans. Disease outbreaks are often linked to flooding. Cases are predicted to increase in coastal areas and small island states with high population density and poor water purification and sanitation [38].

Mycobacterial Pathogens

Tuberculosis is one of the world's most endemic diseases with an estimated 25% of the world infected. Control of the disease has been linked to socioeconomic factors such as public health measure, access to clean water, and sanitation.

In developed countries, disease control is also limited by vaccination, case detection, and antibiotic treatment. Transmission of the disease is by respiratory droplets and is increased in conditions of population crowding or increased indoor residence. Climate change as it influences food sources and water levels may lead to increased population density, poor public health, and, consequently, an increased incidence of tuberculosis. However, research on climate change tuberculosis is limited.

Nontuberculous mycobacteria cause a variety of difficult to treat infections in human, particularly those with underlying lung disease and immunosuppressive states. The pathogens are waterborne. Climate change with its impact on groundwater and wetlands as well as drinking water supplies will likely increase cases of nontuberculous mycobacteria in coming years [39].

Climate Change and Rheumatology

Patients with musculoskeletal conditions have long claimed sensitivity to changes in temperature and humidity. Many patients with arthritis claim that they can predict the weather in their joints. Clinical series have confirmed a relationship between weather and exacerbations of gouty arthritis [40] and rheumatoid arthritis [41] but not osteoarthritis [42]. As discussed above, changes in long-term weather (climate change) will influence both the epidemiology and severity of infectious diseases though effects on the pathogen, the environment, and the host. It is a certainty that climate change will increase the rheumatologic complications of infectious diseases as well. How this unfolds over time will present new challenges to rheumatologists and their patients.

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L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2