Published in final edited form as:
Curr Opin Rheumatol. 2008 July ; 20(4): 480–485. doi:10.1097/BOR.0b013e3282fd6e70.

Osteoarticular infectious complications in patients with primary immunodeficiencies

Katherine A. Bloom*, **Danna Chung***, and **Charlotte Cunningham-Rundles**
The Mount Sinai Medical Center, New York, USA

Abstract

Purpose of review—To describe the incidence and management of various infectious arthritides in selected primary immunodeficiency states.

Recent findings—Joint complications have been a well recognized finding in patients with primary immunodeficiencies for many years. Many are clearly infectious in etiology, but other apparently noninfectious joint abnormalities similar to rheumatoid arthritis have been shown to be due to an underlying infectious trigger. In humoral immunodeficiencies such as common variable immunodeficiency and X-linked agammaglobulinemia, bacterial organisms are the most common causes of infectious arthritis, but mycoplasmas and ureaplasmas are also of particular importance. In nonhumoral immunodeficiencies, noninfectious inflammatory arthritides are more prevalent, although microbiologic organisms have been reported in some cases of arthritis. Lack of appropriate culturing techniques and documentation of infectious agents may underestimate the prevalence of low-virulence infections in these patients.

Summary—Infectious arthritis is a significant comorbidity associated with primary immunodeficiencies and can be the presenting feature for some patients. Prompt examination for common as well as atypical organisms is not only important for the treatment but also crucial to the understanding of the exact etiology of arthritides as a whole in these disorders.

Keywords

immunodeficiency; infectious arthritis; septic joint

Introduction

Primary immunodeficiencies represent a heterogeneous group of genetically based immune defects of the innate and adaptive immune system. The resulting diseases can be defined broadly as disorders of T-cell immunity, B-cell (antibody) production, combined defects, complement, or the phagocytic systems. Given the risk of invasive infections, delay in diagnosing these diseases can have serious consequences including bacterial, fungal or viral infections of the joints, bones, and supporting tissues. The present study will concentrate on the infectious rheumatic complications of the primary immunodeficiencies, focusing on the common infectious organisms involved in selected deficiencies (Table 1), and followed by diagnostic and treatment considerations.

Correspondence to Charlotte Cunningham-Rundles, MD, PhD, Professor of Medicine, Pediatrics and Immunobiology, Mount Sinai School of Medicine, 1425 Madison Avenue, New York, NY 10029, USA, Tel: +1 212 659 9268; fax: +1 212 987 5593; e-mail: E-mail: charlotte.cunningham-rundles@mssm.edu.
*Dr Katherine A. Bloom and Dr Danna Chung contributed equally to the writing of this article.

Infectious arthridites in humoral immunodeficiencies

For somewhat unclear reasons, the majority of infectious complications that involve the joints in immune deficiency are due to defects of antibody production. Humoral immunity is characterized by antibody production against a variety of extracellular microbes that is necessary for their neutralization and elimination. Although patients with primary antibody deficiencies are most susceptible to recurrent infections of the sinopulmonary tract, other infections also occur, including meningitis, osteomyelitis, cellulitis, conjunctivitis, hepatitis, and gastroenteritis [1–4]. Compared with other congenital immune defects, bone and joint infections are seen more commonly in patients with common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) [1–4]. Although occurrence of arthritis in patients with immunoglobulin G (IgG) subclass deficiencies is not well documented, Beard *et al.* [5] analyzed IgG subclass levels in a group of 15 children with septic arthritis and osteomyelitis and discovered that four patients had IgG subclass concentrations below the fifth percentile for age despite normal total immunoglobulin levels, suggesting that minimally impaired antibody production may still have predisposed a number of these children to develop joint infections.

Common joint organisms

The same organisms that commonly infect the sinopulmonary tract in humoral immune deficiency are those isolated from joints – *Staphylococcus aureus* and encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [3]. Bacterial infections of the joint are the most likely reason for acute arthritis in patients with hypogammaglobulinemia and, in some cases, are the presenting symptom that leads to the diagnosis of immune deficiency. For example, Peters *et al.* [6] described a young boy who had two episodes of pneumococcal arthritis with two different serotypes of *S. pneumoniae* at 3 and 5 years of age. Given that streptococcal joint infections are uncommon in children over the age of 2 years, an immunodeficiency was suspected and the child was subsequently diagnosed with XLA. In another case, septic arthritis with *H. influenzae*, an uncommon invasive organism, was the herald infection that led to the diagnosis of CVID in an adult patient reported by Hawkins *et al.* [7].

Mycoplasma and *Ureaplasma* infections

Complicating the diagnosis of septic arthritis is the difficulty of culturing causative organisms in each case. This difficulty in distinguishing actual infections from synovial or joint inflammation can pose a problem for these congenital immune defects. With improved culture methods and more advanced laboratory techniques, atypical agents such as mycoplasmas and ureaplasmas, generally considered nonpathogenic organisms in immunocompetent individuals, have been implicated as the responsible organisms in many cases of arthritis in patients with CVID or XLA [8–14]. Furr *et al.* [10] reported observations on a cohort of 91 patients with hypoglobulinemia followed over 20 years. Twenty-one patients (23%) developed septic arthritis during this time period and either mycoplasmas or ureaplasmas or both were recovered from the joints of eight (38%) of these patients. Franz *et al.* [9] analyzed a cohort of patients with primary antibody deficiency including CVID and XLA who were on regular replacement immunoglobulin therapy. Although no patient developed an acute bacterial arthritis when on treatment, 18 (5%) of the 358 patients developed a chronic arthritis, and mycoplasmas were cultured from synovial fluid or tissue samples in most of these patients. Mycoplasmal arthritis has also been reported as the presenting feature in XLA [9] and CVID [11,13].

Of the 14 species of *Mycoplasma* known to cause human disease, five have been isolated from the joints of patients with hypogammaglobulinemia and arthritis including *Mycoplasma*

pneumoniae [8–11,14], *M. salivarium* [9,10,12], *M. hominis* [9,10,13,15], *M. orale* [16], and *M. felis* [17]. Ureaplasmas are the most frequently isolated organisms and *Ureaplasma urealyticum* has been implicated in numerous reported cases of septic arthritis in patients with antibody deficiency [9,10,15,18–26]. Increased susceptibility to colonization with mycoplasmas in patients with hypogammaglobulinemia has been demonstrated [10] and might be explained by the lack of protective antibodies at mucosal surfaces. The possibility of better mucosal colonization in patients lacking sufficient antibodies may also account for the increased risk of dissemination from the respiratory and urogenital tracts to the joints and other distant sites in these patients. It is not fully understood why *Mycoplasma* species have a tendency to infect the joints of these patients, but in-vitro work has suggested that minor trauma common to large joints attracts neutrophils. Neutrophils have been shown to take up mycoplasmas into phagocytic vacuoles in the absence of specific antibodies where they remain viable and are subsequently released into joint spaces [27]. Additionally, synovial fluid is presumed to be a favorable environment in which mycoplasmas can grow.

Other pathogens

Chronic enteroviral meningoencephalitis used to be a well recognized complication in patients with XLA; in some cases, the chronic clinical syndrome included a dermatomyositis-like illness with joint stiffness and skin changes [28,29]. The chronicity of this infection is illustrated by one patient with XLA and echovirus 11-induced arthritis who developed persistence of virus in joint effusions for 6 months and demonstrated evidence of central nervous system involvement 30 months later [30]. The majority of published studies are on patients who are on immunoglobulin replacement or only on intramuscular immunoglobulin; the widespread use of intravenous immunoglobulin (IVIg) is thought to have almost eradicated enteroviral infections in these patients [31]. Other less common pathogens causing joint infections have been described including *Pneumocystis carinii* (now *jiroveci*) osteomyelitis in CVID [32], *Chlamydia pneumoniae* arthritis in a patient with CVID [33], and adenovirus type 1 joint infection in another patient with immunodeficiency [34].

Noninfectious arthritides in humoral immunodeficiencies

Classical rheumatoid arthritis (RA) may occur in hypogammaglobulinemia, but is uncommon. In an analysis of 248 patients with CVID, five patients had concurrent RA and four had juvenile RA [1,2]. Classical RA is even more uncommon in XLA [35,36], a situation that has attracted attention as removing B-cells by rituximab leads to improvement in RA in immunocompetent individuals [37•].

However, a form of joint inflammation that resembles RA has been seen in 10–30% of patients with CVID of XLA prior to the institution of immunoglobulin therapy [38]. For unclear reasons, immunoglobulin treatment rapidly resolves the joint abnormalities in many cases [39], leading to the assumption that still unrecognized infectious causes are possible. Alternatively, an anti-inflammatory effect of the immunoglobulin may also be responsible for the rapid resolution of these joint arthritides.

Infectious arthritis in other immune deficiency syndromes

Although patients with humoral immunodeficiency are more likely to develop joint, bone and connective tissue infections, and chronic arthritis, other immunodeficiency diseases associated with a lack of sufficient antibody can lead to similar complications. However, as the cases of arthritis in CVID and XLA have described, the infecting organisms have not always been documented, leading to a potential overlap between infectious and noninfectious ases.

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome is an X-linked recessive disorder characterized by eczema, thrombocytopenia, and immunodeficiency with decreased antibody production and T-cell activation and regulatory cell dysfunction. Owing to lack of anticarbohydrate antibody and appropriate regulatory controls, infections and autoimmune and inflammatory complications are commonly noted [40]. In one study [41] of 55 patients, 29% developed arthritis, though this arthritis was classified as nonbacterial joint edema and no organism was identified in this patient group.

Hyperimmunoglobulin M syndrome

X-linked hyperimmunoglobulin M (hyper-IgM) syndrome is another uncommon primary immunodeficiency caused by mutations in the CD40 ligand gene, resulting in defects in CD154 expression, CD40 signaling, and defective isotype switching. Owing to the lack of IgG antibody, patients develop infections with encapsulated organisms similar to those found in XLA and CVID; males with this immune defect are also subject to inflammatory arthritis, often with no clear organism documented. In a study [42] of 56 patients with X-linked hyper-IgM, six patients had arthritis with unclear microbial etiology. Aseptic arthritis has also been described in patients with an autosomal recessive form of hyper-IgM due to mutations in the gene encoding for activation-induced cytidine deaminase (AID) [43].

Interleukin-1 receptor-associated kinase-4 deficiency

Interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency is a more recently described immunodeficiency affecting the toll-like receptor pathways that leads to increased risk of recurrent invasive pyogenic infections such as *S. pneumoniae* [44•]. Given the impaired antibody-mediated and innate immunity, pneumococcus can be harbored in tissue compartments and lead to septic arthritis. Szabo *et al.* [45•] described a boy who developed purulent arthritis of the hip joint at 3 years of age, and later developed meningitis at 5 years of age with the same persistent strain of *S. pneumoniae* serotype 14.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is an inherited disorder of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system that leads to neutrophil dysfunction, predisposing patients to pneumonia and skin infections. Osteomyelitis is another commonly documented complication, affecting 25% of 368 patients in the United States CGD registry and 16% of patients in a recent Italian study [46•]. Organisms common in CGD include *S. aureus*, *Aspergillus*, *Burkholderia cepacia*, *Candida* spp, *Serratia* spp, *Klebsiella*, and *Salmonella* [47]. In most cases, however, these are primarily skeletal versus joint infections, although a predisposing joint infection may have been involved [48].

Diagnosis

In patients with immunodeficiency, infectious arthritis can present as a monoarthritis or a polyarthritis, though multiple joint involvement is usually associated with a delay in diagnosis and treatment [26]. Large joints such as the knees, shoulders, elbows, and hips [9–15,17,18, 25,26] are most frequently affected, although involvement of small joints such as those in the hands and feet has also been described [9–11,14,23]. A purulent effusion is often present in cases with a bacterial etiology and patients are typically acutely ill. However, in mycoplasmal arthritis, extra-articular findings are generally rare and a joint infection with *Mycoplasma* frequently occurs without causing systemic symptoms or purulence in the joint. An interesting feature that has been reported in patients with mycoplasmal arthritis is the presence of

subcutaneous nodules that often occur on the ulnar regions of the forearm and regress when the mycoplasmal arthritis is effectively treated [9,11,13,14].

Synovial fluid from affected joints should be promptly aspirated and cultured. In patients with primary immunodeficiency, early suspicion of a mycoplasmal infection is crucial to ensure that appropriate culture media for mycoplasmas and ureaplasmas are utilized, bearing in mind that certain individual species necessitate special culture conditions. In fact, some mycoplasmal species may require additional nonculture methods such as a polymerase chain reaction assay [22], 16S rRNA sequence analysis [16], or DNA hybridization [23] to identify the particular organism. Cultures may need to be incubated for a minimum of 6 weeks.

Treatment

Treatment of infectious arthritis may necessitate a combination of appropriate antimicrobials, immunoglobulin and, possibly, anti-inflammatory agents. Joint drainage is an important component of treatment in bacterial arthritis and should be performed whenever possible. Therapy should be initiated as soon as possible as a delay in diagnosis and treatment may result in irreversible joint damage [11,13,23]. This complication was illustrated in a case of a woman who initially presented with mycoplasmal arthritis [13]. As the patient had not yet been diagnosed with an immunodeficiency, *Mycoplasma* and *Ureaplasma* were not considered. Effective treatment was delayed and she progressed to develop radiographic evidence of destructive changes of the wrists, carpal bones, knees, hips, shoulders, and ankles.

Antibiotics

The initial choice of antibiotics for acute bacterial arthritis should be based on the most likely organisms causing the infection and the result of the Gram's stain. If *S. aureus* is suspected, treatment with vancomycin should be administered given the increasing incidence of methicillin-resistant *S. aureus*. For other organisms, a third-generation cephalosporin would be the antibiotic of choice until speciation and susceptibility results are obtained. Because mycoplasmas are a common cause of infectious arthritis in patients with primary immunodeficiency, antibiotic treatment against *Mycoplasma* should be initiated early in all cases of bacteriologically negative cultures. The majority of *Mycoplasma* infections respond to standard antibiotic therapy with tetracyclines [12,21]; if necessary, antibiotic treatment can be continued for a prolonged period of 2–6 months in these patients [11,16,18].

Immunoglobulin therapy

Patients with immunodeficiency who are on regular replacement IVIg therapy are at decreased risk of developing acute bacterial arthritis [9]. Nevertheless, published studies [23,26] suggest that, while mycoplasmal arthritis can develop on inadequately dosed IVIg therapy, it can also be seen in patients on standard IVIg [9,16,18,19,25], presumably because of inadequate immune means of clearing these infections. Therefore, careful maintenance of IgG levels within the normal range on standard IVIg may not eliminate the risk of mycoplasmal arthritis in these patients.

Other therapies

Recalcitrant cases of widespread mycoplasmal arthritis due to a delay in diagnosis or the development of antibiotic resistance have been reported [9,15,25]. The rapid development of resistant organisms was illustrated by Lehmer *et al.* [23], who reported an unusual case of *U. urealyticum* arthritis in CVID that was resistant to multiple antibiotics and persisted for 5 years before the patient finally responded to the macrolide antibiotic rosaramicin. However, in cases where there is little or no response to longer courses of various combinations of antibiotics, treatment with hyperimmune animal serum has been shown to be effective [9].

The role of anti-inflammatory agents in infectious arthritis in immunocompromised patients is unclear. Treatment with aspirin was attempted in a patient with XLA with echovirus 11-induced arthritis who failed treatment with IVIg and an intra-articular injection of IVIg with neutralizing titers of echovirus [30]. The patient did have resolution of his joint effusions 3–4 months later, but it remained unclear whether this was due to aspirin, continued treatment with IVIg, or the natural resolution of the disease. In rare instances, such as in patients with Wiskott–Aldrich syndrome, short courses of oral steroids may be indicated, provided appropriate antibiotics are already in place.

Conclusion

Our current knowledge of septic arthritis in patients with primary immunodeficiencies stresses the importance of early detection and antimicrobial intervention. Bacterial organisms are common etiologic agents, whereas nonbacterial organisms are less common but have been reported. For those with antibody deficiency, mycoplasmal involvement is relatively frequent and should be strongly considered in cases of bacteriologically negative cultures of synovial fluid. An impaired immune system can lead to occult and prolonged joint infections, which can cause erosive joint space destruction and possible invasive skeletal and systemic infection. Therefore, an increased suspicion of infectious arthritis in patients with primary immunodeficiency is essential.

Acknowledgments

The present work was supported by grants from the National Institutes of Health (AI-101093, AI-467320, AI-48693 and NIAID Contract 03-22).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 512–513).

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92:34–48. [PubMed: 10413651]
2. Cunningham-Rundles C. Common variable immunodeficiency. Curr Allergy Asthma Rep 2001;1:421–429. [PubMed: 11892068]
3. Hansel TT, Haeney MR, Thompson RA. Primary hypogammaglobulinaemia and arthritis. Br Med J (Clin Res Ed) 1987;295:174–175.
4. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 2006;85:193–202. [PubMed: 16862044]
5. Beard LJ, Ferris L, Ferrante A. Immunoglobulin G subclasses and lymphocyte subpopulations and function in osteomyelitis and septic arthritis. Acta Paediatr Scand 1990;79:599–604. [PubMed: 2386051]
6. Peters TR, Brumbaugh DE, Lawton AR, Crowe JE Jr. Recurrent pneumococcal arthritis as the presenting manifestation of X-linked agammaglobulinemia. Clin Infect Dis 2000;31:1287–1288. [PubMed: 11073766]
7. Hawkins RE, Malone JD, Ebbeling WL. Common variable hypogammaglobulinemia presenting as nontypable Haemophilus influenzae septic arthritis in an adult. J Rheumatol 1991;18:775–776. [PubMed: 1865431]

8. Davis CP, Cochran S, Lisse J, et al. Isolation of Mycoplasma pneumoniae from synovial fluid samples in a patient with pneumonia and polyarthritis. Arch Intern Med 1988;148:969–970. [PubMed: 3128197]
9. Franz A, Webster AD, Furr PM, Taylor-Robinson D. Mycoplasmal arthritis in patients with primary immunoglobulin deficiency: clinical features and outcome in 18 patients. Br J Rheumatol 1997;36:661–668. [PubMed: 9236676]
10. Furr PM, Taylor-Robinson D, Webster AD. Mycoplasmas and ureaplasmas in patients with hypogammaglobulinaemia and their role in arthritis: microbiological observations over twenty years. Ann Rheum Dis 1994;53:183–187. [PubMed: 8154936]
11. Johnston CL, Webster AD, Taylor-Robinson D, et al. Primary late-onset hypogammaglobulinaemia associated with inflammatory polyarthritis and septic arthritis due to Mycoplasma pneumoniae. Ann Rheum Dis 1983;42:108–110. [PubMed: 6830319]
12. So AK, Furr PM, Taylor-Robinson D, Webster AD. Arthritis caused by Mycoplasma salivarium in hypogammaglobulinaemia. Br Med J (Clin Res Ed) 1983;286:762–763.
13. Steuer A, Franz A, Furr PM, et al. Common variable immunodeficiency presenting as a Mycoplasma hominis septic arthritis. J Infect 1996;33:235–237. [PubMed: 8945717]
14. Taylor-Robinson D, Gumpel JM, Hill A, Swannell AJ. Isolation of Mycoplasma pneumoniae from the synovial fluid of a hypogammaglobulinaemic patient in a survey of patients with inflammatory polyarthritis. Ann Rheum Dis 1978;37:180–182. [PubMed: 646469]
15. Heilmann C, Jensen L, Jensen JS, et al. Treatment of resistant mycoplasma infection in immunocompromised patients with a new pleuromutilin antibiotic. J Infect 2001;43:234–238. [PubMed: 11869060]
16. Paessler M, Levinson A, Patel JB, et al. Disseminated Mycoplasma orale infection in a patient with common variable immunodeficiency syndrome. Diagn Microbiol Infect Dis 2002;44:201–204. [PubMed: 12458129]
17. Bonilla HF, Chenoweth CE, Tully JG, et al. Mycoplasma felis septic arthritis in a patient with hypogammaglobulinemia. Clin Infect Dis 1997;24:222–225. [PubMed: 9114151]
18. Webster AD, Taylor-Robinson D, Furr PM, Asherson GL. Mycoplasmal (ureaplasma) septic arthritis in hypogammaglobulinaemia. Br Med J 1978;1:478–479. [PubMed: 626841]
19. Stuckey M, Quinn PA, Gelfand EW. Identification of Ureaplasma urealyticum (T-strain Mycoplasma) in patient with polyarthritis. Lancet 1978;2:917–920. [PubMed: 81929]
20. Kraus VB, Baraniuk JN, Hill GB, Allen NB. Ureaplasma urealyticum septic arthritis in hypogammaglobulinemia. J Rheumatol 1988;15:369–371. [PubMed: 3361546]
21. Jorup-Ronstrom C, Ahl T, Hammarstrom L, et al. Septic osteomyelitis and polyarthritis with ureaplasma in hypogammaglobulinemia. Infection 1989;17:301–303. [PubMed: 2599651]
22. Lee AH, Ramanujam T, Ware P, et al. Molecular diagnosis of Ureaplasma urealyticum septic arthritis in a patient with hypogammaglobulinemia. Arthritis Rheum 1992;35:443–448. [PubMed: 1567493]
23. Lehmer RR, Andrews BS, Robertson JA, et al. Clinical and biological characteristics of Ureaplasma urealyticum induced polyarthritis in a patient with common variable hypogammaglobulinaemia. Ann Rheum Dis 1991;50:574–576. [PubMed: 1888200]
24. Forgacs P, Kundsin RB, Margles SW, et al. A case of Ureaplasma urealyticum septic arthritis in a patient with hypogammaglobulinemia. Clin Infect Dis 1993;16:293–294. [PubMed: 8443311]
25. Asmar BI, Andresen J, Brown WJ. Ureaplasma urealyticum arthritis and bacteremia in agammaglobulinemia. Pediatr Infect Dis J 1998;17:73–76. [PubMed: 9469401]
26. Frangogiannis NG, Cate TR. Endocarditis and Ureaplasma urealyticum osteomyelitis in a hypogammaglobulinemic patient. A case report and review of the literature. J Infect 1998;37:181–184. [PubMed: 9821094]
27. Webster AD, Furr PM, Hughes-Jones NC, et al. Critical dependence on antibody for defence against mycoplasmas. Clin Exp Immunol 1988;71:383–387. [PubMed: 3383447]
28. Wilfert CM, Buckley RH, Mohanakumar T, et al. Persistent and fatal central-nervous-system ECHOvirus infections in patients with agammaglobulinemia. N Engl J Med 1977;296:1485–1489. [PubMed: 301244]

29. Thyss A, el Baze P, Lefebvre JC, et al. Dermatomyositis-like syndrome in X-linked hypogammaglobulinemia. Case-report and review of the literature. Acta Derm Venereol 1990;70:309–313. [PubMed: 1977255]
30. Ackerson BK, Raghunathan R, Keller MA, et al. Echovirus 11 arthritis in a patient with X-linked agammaglobulinemia. Pediatr Infect Dis J 1987;6:485–488. [PubMed: 3601497]
31. Misbah SA, Spickett GP, Ryba PC, et al. Chronic enteroviral meningoencephalitis in agammaglobulinemia: case report and literature review. J Clin Immunol 1992;12:266–270. [PubMed: 1512300]
32. Esolen LM, Fasano MB, Flynn J, et al. Pneumocystis carinii osteomyelitis in a patient with common variable immunodeficiency. N Engl J Med 1992;326:999–1001. [PubMed: 1545853]
33. Ardeniz O, Gulbahar O, Mete N, et al. Chlamydia pneumoniae arthritis in a patient with common variable immunodeficiency. Ann Allergy Asthma Immunol 2005;94:504–508. [PubMed: 15875533]
34. Fraser KJ, Clarris BJ, Muirden KD, et al. A persistent adenovirus type 1 infection in synovial tissue from an immunodeficient patient with chronic, rheumatoid-like polyarthritis. Arthritis Rheum 1985;28:455–458. [PubMed: 2985091]
35. Hermaszewski R, Ratnavel R, Webster AD, Denman AM. Rheumatoid arthritis in a patient with primary hypogammaglobulinaemia. Br J Rheumatol 1993;32:636–639. [PubMed: 8339142]
36. Verbruggen G, De BS, Deforce D, et al. X linked agammaglobulinaemia and rheumatoid arthritis. Ann Rheum Dis 2005;64:1075–1078. [PubMed: 15564308]
37•. Kwan-Morley J, Albert D. B-cell inhibitors as therapy for rheumatoid arthritis: an update. Curr Rheumatol Rep 2007;9:401–406.406 [PubMed: 17915096] A comprehensive review of B-cell-directed therapy in the treatment of rheumatoid arthritis with a specific focus on rituximab, though other approaches are also discussed.
38. Lee AH, Levinson AI, Schumacher HR Jr. Hypogammaglobulinemia and rheumatic disease. Semin Arthritis Rheum 1993;22:252–264. [PubMed: 8484132]
39. Webster AD, Loewi G, Dourmashkin RD, et al. Polyarthritis in adults with hypogammaglobulinaemia and its rapid response to immunoglobulin treatment. Br Med J 1976;1:1314–1316. [PubMed: 57818]
40. Schurman SH, Candotti F. Autoimmunity in Wiskott–Aldrich syndrome. Curr Opin Rheumatol 2003;15:446–453. [PubMed: 12819473]
41. Dupuis-Girod S, Medioni J, Haddad E, et al. Autoimmunity in Wiskott–Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 2003;111 (5 Pt 1):e622–e627. [PubMed: 12728121]
42. Levy J, Espanol-Boren T, Thomas C, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 1997;131(1 Pt 1):47–54. [PubMed: 9255191]
43. Quartier P, Bustamante J, Sanal O, et al. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to activation-induced cytidine deaminase deficiency. Clin Immunol 2004;110:22–29. [PubMed: 14962793]
44•. Ku CL, von BH, Picard C, et al. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med 2007;204:2407–2422.2422 [PubMed: 17893200] The authors summarize their diagnosis of 28 patients with IRAK-4 deficiency by blood testing of TLR responses, and review the clinical infections and disease course of these patients. IRAK-4-dependent TLRs and IL1Rs provide vital immunity against pyogenic bacteria, especially *S. pneumoniae*.
45•. Szabo J, Dobay O, Erdos M, et al. Recurrent infection with genetically identical pneumococcal isolates in a patient with interleukin-1 receptor-associated kinase-4 deficiency. J Med Microbiol 2007;56(Pt 6):863–865.865 [PubMed: 17510276] Case report of a boy with IRAK-4 deficiency found to have genetic linkage of *S. pneumoniae* serotype 14 isolates in hip arthritis and meningitis at two different ages, indicating possible persistent strains of pneumococcal infection in this group of patients with immunodeficiency.
46•. Martire B, Rondelli R, Soresina A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: An Italian multicenter study. Clin Immunol 2008;126:155–164.164 [PubMed: 18037347] Given the wide range of clinical variability in patients with CGD, this multicenter retrospective survey provides an up-to-date review of clinical and immunological features in 60 patients.

47. Johnston RB Jr. Clinical aspects of chronic granulomatous disease. Curr Opin Hematol 2001;8:17–22. [PubMed: 11138621]

48. Sponseller PD, Malech HL, McCarthy EF Jr, et al. Skeletal involvement in children who have chronic granulomatous disease. J Bone Joint Surg Am 1991;73:37–51. [PubMed: 1985993]

Table 1

Organisms common in osteoarticular infections in immunodeficient patients

Antibody deficiencies	*Staphylococcus aureus*[a]
X-linked agammaglobulinemia	*Streptococcus pneumoniae*[a]
Common variable immune deficiency	*Haemophilus influenzae*[a]
IgG subclass defects	*Mycoplasma*[a]
	Ureaplasma[a]
	Echovirus[a]
Chronic granulomatous disease	*Staphylococcus aureus*
	Aspergillus[a]
	Burkholderia spp
	Serratia spp[a]
	Candida spp
	Salmonella
	Escherichia coli
Interleukin-1 receptor-associated kinase-4 deficiency	*Staphylococcus aureus*
	Streptococcus pneumoniae[a]

[a]Documented isolation from joints and/or bone in published literature.

IgG, immunoglobulin G.