Infectious Arthritis

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Septic Arthritis

A 72-year-old male with diabetes presents with 1 day of left knee pain and swelling. His symptoms began suddenly and have been worsening. He describes severe pain throughout the entire knee; he is unable to bear weight. He reports feeling hot, but he is unsure if he has had a fever. On exam, he has a warm and palpable effusion in the left knee. What is the most important next step in diagnosis?

The history and exam are concerning for septic arthritis, which is typically due to a bacterial infection. Many different bacteria can cause osteoarticular infections (Table 11.1). The most common is *Staphylococcus aureus*, though Streptoccocal species are also frequently reported [1]. Gram-negative bacteria

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Table 11.1 Bacteria causing septic arthritis

Bacteria	Comment
Staphylococcus aureus	Most common
Streptococcus pneumonia	Do not need to have a concurrent pneumonia
Neisseria gonorrhea	Common in younger patients, two phenotypes: purulent arthritis or triad of tenosynovitis, dermatitis, and polyarthralgias (discussed later)
Gram negative (e.g., *E. coli*)	Usually seen in immunocompromised patients
Lyme	Can migrate and self-resolve (discussed later)

are less common but can be seen in immunocompromised patients. Additionally, *Neisseria gonorrhea* deserves special mention as it is the most common cause of septic arthritis in younger sexually active adults. In addition to bacterial infections, mycobacterial and fungal organisms should be considered in the immunocompromised patient with an indolent progressive arthritis (discussed later). The knee is by far the most common joint affected (~50% of cases); other common involved joints include hip, ankle, elbow, wrist, and shoulder [2]. Septic arthritis is typically monoarticular, but polyarticular disease can be seen in 10–20% of cases [3]. Major risk factors for septic arthritis include age (both very young and elderly), immunosuppression, diabetes, intravenous drug use, dialysis dependence, and importantly, a history of joint prosthesis; however, it should be noted that approximately 20% of patients do not have any identifiable risk factors. The overall incidence of septic arthritis is increasing, especially among the elderly [4].

Bacterial joint infections can cause significant joint destruction within 24–48 hours; early identification and initiation of appropriate therapy is crucial to joint preservation as well as patient survival. Of note, there are no vital signs or serum lab values that can appropriately diagnose septic arthritis; fever and leukocytosis, for example, are seen in only about half of patients with septic arthritis [5]. Elevated inflammatory markers are expected, but this does

not distinguish septic arthritis from the most common mimickers, notably crystalline arthropathies (gout or acute calcium pyrophosphate deposition disease arthropathy). Importantly, although almost all joints are seeded hematogenously, blood cultures are positive in only about 50% of cases.

In contrast to peripheral blood tests, a joint aspiration is indispensable for the diagnosis of septic arthritis and is the most important next step in the workup of the above patient. If this cannot be done in the office, the patient should be sent urgently to the Emergency Room. The likelihood of septic arthritis increases with a higher synovial fluid white blood cell count [6], but the diagnosis is only confirmed by culture of the organism from the joint fluid.

Septic arthritis is treated initially in the hospital setting with IV antibiotics for 4–6 weeks. Additionally, as the infection can be considered a closed-space infection like an abscess, drainage of the affected joint—most commonly with surgical arthroscopy—is also necessary [7]. The overall mortality of septic arthritis is about 10–15%, and about a third of patients will have poor joint outcomes [8]. Age greater than 65 is a major risk factor for both mortality and lasting joint damage in septic arthritis [5].

Disseminated Gonococcal Infection

A 22-year-old female presents with 1 week of migratory polyarticular joint pain and fevers. She first noticed pain and swelling of the right knee, such that it limited her ambulation. There was a minimal response to ibuprofen. A few days later, she noticed swelling and pain in the left wrist and hand; at that time, it was difficult to get dressed in the morning and open doorknobs. She has felt febrile. She denies any sore throat. On exam, she has warmth of the right knee and left wrist, as well as pain in the fingers with passive flexion. You also note purpuric pustular skin lesions around the ankles and on the volar fingers. What is the most likely diagnosis?

This patient is presenting with an acute asymmetric polyarthritis. The differential includes autoimmune, crystalline, or infectious causes, as well as serum sickness due to a new medication. As in the previous case, a joint aspiration would be the best next step. However, the symptoms of an acute migratory polyarthritis, with notable tenosynovitis (as represented by pain with passive ROM of the fingers), and purpuric pustular skin lesions, in a younger patient, is most consistent with disseminated gonococcal infection (DGI). DGI can occur phenotypically in two ways [9]. The first, as described above, is with fever, tenosynovitis, and dermatitis. Characteristic cutaneous lesions are small purpuric macules on the hands and feet [10]. DGI can also present with a more classic monoarticular septic arthritis. Less than 5% of primary gonococcal infections will disseminate [11]; however, the primary infection is often asymptomatic so the lack of mucosal symptoms (e.g., urethritis) cannot be used to rule out the disease. Patients with inherited complement deficits are at high risk for DGI, while menstruating, pregnant and recently post-partum women are also at increased risk. The incidence of gonococcal infections has been decreasing but remains high in certain populations such as men who have sex with men (MSM).

The diagnosis of DGI is made by finding evidence of gonorrhea in a patient with a compatible clinical picture. Blood cultures processed on Thayer-Martin media should be obtained; nucleic acid amplification testing (NAAT) from specimens from all three mucosal sites (pharyngeal, urogenital, and rectal) should also be performed. Importantly, patients with DGI can have evidence of gonorrhea even at asymptomatic sites; so, it is crucial to sample all potential sites of mucosal infection. Synovial fluid should be sent for cell count, differential, gram stain and culture as well as NAAT.

Treatment of DGI is typically intramuscular or intravenous ceftriaxone daily for 7–14 days with a single dose of azithromycin 1000 mg. Drug resistance among gonococcal isolates is growing, and treatment with tetracyclines and especially fluoroquinolones is no longer recommended [12].

Acute Rheumatic Fever

A 33-year-old female patient originally from Brazil presents with 1 week of fevers, pain, and swelling of multiple joints. Originally, she endorsed pain in the right ankle; subsequently the pain spread to her left knee and left wrist, and her right ankle spontaneously improved. She has been taking naproxen with some improvement in symptoms. She notes a history of "rheumatism" for which she has had to see a cardiologist in the past, and a low pitch diastolic murmur is heard at the apex on exam today. She endorses a sore throat in the weeks prior to her joint symptoms. You are concerned about acute rheumatic fever; however, a rapid strep test in the office is negative. What are the appropriate next diagnostic steps?

Acute rheumatic fever (ARF) is an immunological reaction to group A strep (GAS) pharyngitis; symptoms typically occur 2–4 weeks following the primary infection and can consist of fevers, arthritis, carditis, erythema marginatum (an evanescent, annular pink/red rash with slightly raised red border, most common on the trunk and limbs), chorea, and subcutaneous nodules. Importantly, not all patients—especially children—recall a preceding sore throat [13]. At presentation throat cultures and rapid strep tests are usually negative as in the above patient, so evidence of a recent GAS infection is typically made serologically with positive antistreptolysin or anti-DNase titers [14]. ARF is very uncommon in the United States but can be seen in patients immigrating from other counties. It is also more common in patients with previous episodes of rheumatic fever, as in the patient above.

The arthritis of ARF is described as migratory or additive as it spreads from joint to joint. Large/medium size joints such as the knee, ankle, elbow, and wrist are most commonly affected; each individual joint will have symptoms for a few days to a week. It typically responds well to aspirin or NSAIDs [15].

The diagnosis ARF is made using the Jones Criteria, which were updated in 2015 and now distinguish between patients from high and low prevalence countries [16]. Evidence of a recent GAS infection (typically made via serology) is required for diagnosis.

Eradication of GAS with antibiotics is recommended, even if the patient has no current evidence of pharyngitis, as well as screening and treatment of household contacts with group A streptococcus positive throat cultures. The arthritis of ARF is treated symptomatically, typically with aspirin or NSAIDs, and should resolve within 4 weeks without any sequalae [15].

The most problematic complication of ARF by far is rheumatic heart disease (RHD). Although the carditis of rheumatic fever can affect any structure in the heart, valvular disease is typically the most clinically relevant; RHD is the most common cause of acquired valvular disease in the world and causes 275,000 deaths per year [17]. Thus, patients with a history of ARF should receive prophylaxis against future strep infections at least until age 21 (and even longer if there is a history of RHD), since these patients at high risk for recurrent ARF attacks upon re-exposure to GAS, and each subsequent attack typically worsens RHD.

Lyme Arthritis

A 52-year-old male presents with 1 week of swelling, redness, and pain of the right knee. There was no precipitating trauma. The pain and swelling have been gradually increasing, to the point that it is difficult to fully flex his knee. He can ambulate but with difficulty. He denies any fevers or chills, night sweats, unintentional weight loss, or rashes. Other than a history of hypertension, he has no significant medical history; however, he notes that a few weeks prior he had similar symptoms of pain and swelling in the left knee that self-resolved after 5 days. He goes hunting frequently but denies any known tick bites. Bedside ultrasound shows a large right knee effusion with an associated Baker's cyst. How should he be evaluated and treated?

Lyme borreliosis is caused by the spirochete bacteria *Borrelia burgdorferi* and is transmitted to humans by *Ixodes* ticks. Lyme disease is the most common tick-borne illness in the United

States, and it is estimated that reported cases are only approximately 10% of actual cases. Currently, the vast majority of Lyme cases are seen in only a few states, mostly in the Northeast but also in the Upper Midwest [18]. The incidence of Lyme is expected to rise due to changes in habitats favorable to *Ixodes* expansion [19].

Lyme borreliosis has well-defined clinical stages: early localized, early disseminated, and late disseminated. Approximately 80% of patients with Lyme borreliosis develop the characteristic centrifugally expanding erythematous rash known as erythema migrans at the site of the tick bite (usually days afterward). EM rashes are typically minimally painful or pruritic, and thus the rash may not be recognized; it can be accompanied by fevers, myalgias, and arthralgias. EM rashes self-resolve after about 30 days. Days to weeks after the initial infection in the skin, the bacteria will disseminate and can cause further cutaneous, neurologic, or cardiovascular symptoms.

Weeks to months after the initial infection, Lyme arthritis can occur. Notably this phase is characterized by a true inflammatory arthritis, with redness and swelling of the affected joint (not just joint pain). It is estimated that 60% of patients with early Lyme disease will progress to Lyme arthritis in the absence of antibiotic treatment [20]. Interestingly, in the current era, many patients with Lyme arthritis do *not* report a history of erythema migrans since most patients with EM are diagnosed quickly and cured with antibiotic therapy; thus, the absence of a rash consistent with EM cannot rule out the diagnosis. Lyme arthritis typically presents with intermittent episodes of joint swelling primarily of the large joints (especially the knee), often self-resolving [21].

Lyme borreliosis is diagnosed serologically in patients with compatible clinical symptoms. A two-step algorithm is recommended by the Centers for Disease Control (CDC); traditionally this has been an initial enzyme-linked immunosorbent assay (ELISA) follow by confirmatory Western blot [18]. Patients with Lyme arthritis, as in the patient above, are universally found to have almost all ten tested IgG bands on the Western blot (testing

joint fluid for Lyme DNA via polymerase chain reaction (PCR) is not recommended). In 2019, the CDC updated its recommendation to include tests with ELISA for both the screening and confirmatory testing [22], with the goal to increase the sensitivity in early infection. There is a significant rate of overdiagnosis of Lyme driven by the use of serologic testing in patients without compatible clinical features of the disease [23].

Lyme disease is treated with antibiotic therapy. Isolated erythema migrans is treated with oral antibiotics: typically doxycycline for 10 days; or amoxicillin (if pregnant) for 14 days, whereas neurologic or cardiac disease is treated for 4 weeks, usually with intravenous ceftriaxone. Lyme arthritis is treated with 4 weeks of antibiotics, though notably almost half of patients require another round of treatment [21]. Of note, about 10% of patients with Lyme arthritis are antibiotic refractory, in that they continue to have evidence of joint inflammation despite appropriate antibiotic therapy. In those patients, evidence does not suggest a persistent infection but rather the triggering of local autoimmunity [24], and they are treated with anti-inflammatory and immunosuppressive therapy.

There are several misconceptions about Lyme borreliosis. The most pernicious is that Lyme disease can cause persistent infection requiring long-term antibiotic therapy. A small percentage of patients who have been appropriately treated for Lyme disease will develop nonspecific symptoms of fatigue, headache, joint and muscle pain, in the absence of objective markers of inflammation (e.g., joint swelling). This is known as Post-Lyme Disease Syndrome, though it is unclear if these symptoms occur at a higher rate than the background risk in the general population [25]. What is clear is that chronic antibiotic therapy is not more effective than placebo in ameliorating these symptoms [26]. Unfortunately, a large industry has sprouted to inappropriately diagnose patients with “chronic Lyme” and offer unproven and potentially harmful therapies [27]. The American College of Rheumatology does not recommend testing for Lyme disease in patients without objective evidence of joint inflammation [28].

Chikungunya Virus Infection

A 27-year-old female presents with severe polyarticular pain in the axial and peripheral joints over the last 24 hours, with associated high fevers and a diffuse maculopapular rash. The pain is severe enough that it is difficult to even get out of bed. She has never had anything like this before. Two days ago, she returned from a vacation in Turks and Caicos. What lab tests should be sent?

The patient's incapacitating joint pain, along with systemic symptoms and an appropriate exposure history, is characteristic of chikungunya virus infection. Chikungunya virus is an alphavirus spread by the *Aedes* mosquitos. Although chikungunya was first identified in the 1950s in Tanzania ("Chikungunya" means "that which bends up" in the Makonde language, describing the contorted position of the affected patients) [29], the disease was limited to sporadic outbreaks in sub-Saharan Africa until 2004, when a large-scale epidemic developed on islands on the Indian ocean, India, Southeast Asia, and China. Chikungunya was thought to be limited to the tropics until an outbreak in Italy in 2007. The disease subsequently spread to the Americas in 2013, and has since exploded in incidence, infecting millions of people in virtually all South American, Central American, and Caribbean countries [30]. Local transmission has been reported in the United States, but the majority of cases are seen in returning travelers as in the patient above [31]. The incubation period is usually 2–4 days but can be as long as 2 weeks.

Most patients infected with chikungunya become acutely symptomatic, with a high fever, maculopapular rash, and debilitating joint pain affecting both the peripheral and axial skeleton. Chikungunya can be difficult to differentiate from Dengue fever, though joint symptoms are typically more prominent in chikungunya and thrombocytopenia is more common with Dengue [32]. The diagnosis is made with serum PCR when testing is performed with symptoms between 1 and 7 days and positive serologies in those with symptoms for 8 or more days. Acute therapy is supportive with NSAIDs and hydration.

Although most symptoms of chikungunya resolve in 1–2 weeks, and the mortality rate appears to be lower than other alphaviruses like Dengue, importantly joint pain and swelling can persist for months or even years in a up to 40% of patients [33]. In those patients, evidence suggests that the persistent inflammation is related to triggering of immunologic abnormalities, and not persistent viral infection [34]; patients can even develop erosions mimicking rheumatoid arthritis [35]. These patients are therefore treated like rheumatoid arthritis, using disease-modifying agents like methotrexate [36], and even TNF-alpha inhibitors.

Parvovirus Infection

A 45-year-old female presents with 7 days of pain and stiffness in the small joints of her hands. There is associated swelling most prominent in the metacarpal phalangeal joints (MCPs). Upon waking, she is stiff for about 2 hours and has difficulty with morning tasks like buttoning her clothes or squeezing toothpaste. She has never had any similar symptoms in the past. Prior to the development of these symptoms, she described a few days of low-grade fevers, malaise, and coryza. She denies a rash. On exam, she has swelling and tenderness of the MCPs and PIPs. What is the most likely diagnosis?

Although many viruses can cause diffuse arthralgias, typically in the setting of fevers and myalgias (e.g., influenza, Epstein-Barr virus, or Cytomegalovirus), it is uncommon for viruses to cause a true arthritis (characterized by joint swelling and redness) in which the joint involvement dominates the clinical picture. SARS-Cov-2, the virus that causes COVID-19, is also not thought to cause a true inflammatory arthritis. An exception to this is the single-stranded DNA virus parvovirus B19, which in adults can cause an acute small joint arthritis resembling rheumatoid arthritis. Adults with exposure to young children, for example preschool teachers, are at highest risk of infection, especially in the winter months. As in the scenario above, patients usually have prodromal flu-like symptoms and then present with symmetric pain and stiffness in the small joints of the hands and wrist, but

large joints such as knees, shoulders, and elbows can also be affected [37]. Of note, while the "slapped cheek" rash (erythema infectiosum) is a characteristic feature of acute parvovirus infection in children (in which case it is also called Fifth disease), this rash is uncommon in adults.

Many cases of parvovirus are asymptomatic, and most adults typically have serologic evidence of previous infection with positive IgG levels. The diagnosis of acute parvovirus infection is made with positive IgM serologies. The joint symptoms can be managed with NSAIDs and are typically short-lived, resolving over a few weeks. Unlike with chikungunya infection as above, there is no evidence linking parvovirus to the development of a chronic inflammatory arthritis [38]. Of note, parvovirus infection can transiently elevate rheumatoid factor, which can make the distinction between acute parvovirus and early rheumatoid arthritis difficult. Persistent arthritis beyond 6 weeks as well as a positive test for antibodies to citrullinated proteins (CCP antibody test) would suggest rheumatoid arthritis.

Osteoarticular Tuberculosis

A 45-year-old HIV positive male comes to your office for 4 months of right knee pain. The pain began gradually but has been worsening. He has noticed swelling and difficulty bending his knee. He is able to ambulate but with difficulty, and you notice a limp as he walks into the exam room. He denies any fevers, night sweats, cough, or unintentional weight loss. The patient admits to noncompliance with his HIV regimen; he is unsure of his last CD4 count and has not seen his infectious disease doctor in a few years. On exam, the knee is swollen but minimally red and tender; the range of motion is preserved. What diagnosis should be considered?

Given his immunocompromised state, this patient is at risk for uncommon opportunistic osteoarticular infections, including fungal and mycobacterial infections. All can present with a subacute to chronic inflammatory arthritis. In this case, synovial biopsy eventually grew mycobacterium tuberculosis (MTB). According

to the WHO, about 1/3 of persons living with HIV are co-infected with MTB [39].

The spine is the most common site for osteoarticular tuberculosis infections, but peripheral arthritic involvement is also a frequent complication [40]. Unlike pyogenic bacteria (e.g., staphylococcal) that present acutely, peripheral joint infections of mycobacteria will develop indolently over months. Notably, only about half of patients with peripheral joint tuberculosis will have fevers, and only a quarter will have night sweats or weight loss [40]; thus, the absence of these symptoms cannot be used to rule out the diagnosis.

Serum blood tests are unlikely to be helpful in this case. A positive interferon-gamma release assay does not distinguish between latent and active tuberculosis infection. Additionally, a negative test cannot rule out active MTB. The diagnosis can be established by culturing MTB from another site in the setting of compatible osteoarticular features, or by synovial culture. Synovial fluid aspiration would be expected to show inflammatory fluid (e.g. 15–30,000 WBCs), but the sensitivity of AFB staining for diagnosis of joint MTB is very poor [41]. Culture of synovial fluid is more sensitive, but often a synovial biopsy and tissue culture is needed for definitive diagnosis. Nucleic acid amplification testing can add in the diagnosis of TB but do not have FDA approval for testing in synovial fluid. Osteoarticular tuberculosis is treated similarly to pulmonary tuberculosis, with multiple drug therapy over 6–9 months [42].

References

1. Dubost JJ, Couderc M, Tatar Z, et al. Three-decade trend in the distribution of organisms causing septic arthritis in native joints. Joint Bone Spine. 2014;81(5):438–40.
2. Kaandorp CJ, Dinant HJ, van de Laar MA, et al. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. Ann Rheum Dis. 1997;56:470–5.
3. Dubost JJ, Fis I, Denis P, et al. Polyarticular septic arthritis. Medicine (Baltimore). 1993;72:296–310.

4. Rutherford AI, et al. A population study of the reported incidence of native joint septic arthritis in the United Kingdom between 1998 and 2013. Rheumatology (Oxford). 2016;55(12):2176–80.
5. Weston VC, Jones AC, Bradbury N, et al. Clinical features and outcome of septic arthritis in a single UK Health District 1982–1991. Ann Rheum Dis. 1999;58:214–9.
6. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA. 2007;297(13):1478–88.
7. Ross JJ. Septic arthritis of native joints. Infect Dis Clin N Am. 2017;31(2):203–18.
8. Kaandorp CJ, Krijnen P, Moens HJ, Habbema JD, van Schaardenburg D. The outcome of bacterial arthritis: a prospective community-based study. Arthritis Rheum. 1997;40(5):884–92.
9. O'Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. Medicine (Baltimore). 1983;62(6):395–406.
10. Ghosn SH, Kibbi A-G. Cutaneous gonococcal infections. Clin Dermatol. 2004;22:476–80.
11. Rice PA. Gonococcal arthritis (disseminated gonococcal infection). Infect Dis Clin N Am. 2005;19(4):853–61.
12. Unemo M, Seifert HS, Hook EW 3rd, Hawkes S, Ndowa F, Dillon JR. Gonorrhoea. Nat Rev Dis Primers. 2019;5(1):79.
13. Veasy LG, Wiedmeier SE, Orsmond GS, Ruttenberg HD, Boucek MM, Roth SJ, Tait F, Thompson JA, Daly JA, Kaplan EL, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med. 1987;316(8):421–7.
14. Steer AC, Smeesters PR, Curtis N. Streptococcal serology: secrets for the specialist. Pediatr Infect Dis J. 2015;34(11):1250–2.
15. Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet. 2018;392(10142):161–74.
16. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, Remenyi B, Taubert KA, Bolger AF, Beerman L, Mayosi BM, Beaton A, Pandian NG, Kaplan EL, American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American HeartAssociation. Circulation. 2015;131(20):1806–18.
17. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132(17):1667–78.
18. John TM, Taege AJ. Appropriate laboratory testing in Lyme disease. Cleve Clin J Med. 2019;86(11):751–9.

19. Schoen RT. Challenges in the diagnosis and treatment of Lyme disease. Curr Rheumatol Rep. 2020;22(1):3.
20. Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. Ann Intern Med. 1987;107(5):725–31.
21. Bockenstedt LK, Wormser GP. Review: unraveling Lyme disease. Arthritis Rheumatol. 2014;66(9):2313–23.
22. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep. 2019;68:703.
23. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of over diagnosis and overtreatment of Lyme disease: an observational study. Ann Intern Med. 1998;128(5):354–62.
24. Lochhead RB, Strle K, Kim ND, Kohler MJ, Arvikar SL, Aversa JM, Steere AC. MicroRNA expression shows inflammatory dysregulation and tumor-like proliferative responses in joints of patients with postinfectious Lyme arthritis. Arthritis Rheumatol. 2017;69(5):1100–10.
25. Cerar D, Cerar T, Ruzić-Sabljić E, Wormser GP, Strle F. Subjective symptoms after treatment of early Lyme disease. Am J Med. 2010;123(1):79–86.
26. Melia MT, Auwaerter PG. Time for a different approach to Lyme disease and long-term symptoms. N Engl J Med. 2016;374(13):1277–8.
27. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP, AdHoc International Lyme Disease Group, Agger WA, Artsob H, Auwaerter P, Dumler JS, Bakken JS, Bockenstedt LK, Green J, Dattwyler RJ, Munoz J, Nadelman RB, Schwartz I, Draper T, McSweegan E, Halperin JJ, Klempner MS, Krause PJ, Mead P, Morshed M, Porwancher R, Radolf JD, Smith RP Jr, Sood S, Weinstein A, Wong SJ, Zemel L. A critical appraisal of "chronic Lyme disease". N Engl J Med. 2007;357(14):1422–30.
28. Yazdany J, Schmajuk G, Robbins M, Daikh D, Beall A, Yelin E, Barton J, Carlson A, Margaretten M, Zell J, Gensler LS, Kelly V, Saag K, King C, American College of Rheumatology Core Membership Group. Choosing wisely: the American College of Rheumatology's top 5 list of things physicians and patients should question. Arthritis Care Res (Hoboken). 2013;65(3):329–39.
29. Vu DM, Jungkind D, LaBeaud AD. Chikungunya virus. Clin Lab Med. 2017;37(2):371–82.
30. Weaver SC, Lecuit M. Chikungunya virus infections. N Engl J Med. 2015;373(1):94–5.
31. Lindsey NP, Staples JE, Fischer M. Chikungunya virus disease among travelers-United States, 2014–2016. Am J Trop Med Hyg. 2018;98(1):192–7.
32. Hyle EP, Alame D. Case records of the Massachusetts General Hospital. Case 13-2015. A 27-year-old woman with arthralgias and a rash. N Engl J Med. 2015;372(17):1657–64.

33. Amaral JK, Bilsborrow JB, Schoen RT. Chronic chikungunya arthritis and rheumatoid arthritis: what they have in common. Am J Med. 2020;133(3):e91–7.
34. Chang AY, KAO M, Encinales L, Reid SP, Acuña M, Encinales C, Matranga CB, Pacheco N, Cure C, Shukla B, Ruiz Arteta T, Amdur R, Cazares LH, Gregory M, Ward MD, Porras A, Rico Mendoza A, Dong L, Kenny T, Brueggemann E, Downey LG, Kamalapathy P, Lichtenberger P, Falls O, Simon GL, Bethony JM, Firestein GS. Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. Arthritis Rheumatol. 2018;70(4):585–93.
35. Malvy D, Ezzedine K, Mamani-Matsuda M, et al. Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. BMC Infect Dis. 2009;9:200.
36. Amaral JK, Sutaria R, Schoen RT. Treatment of chronic chikungunya arthritis with methotrexate: a systematic review. Arthritis Care Res (Hoboken). 2018;70(10):1501–8.
37. Moore TL. Parvovirus-associated arthritis. Curr Opin Rheumatol. 2000;12:289–94.
38. Speyer I, Breedveld FC, Dijkmans BA. Human parvovirus B19 infection is not followed by inflammatory joint disease during long term follow-up. A retrospective study of 54 patients. Clin Exp Rheumatol. 1998;16(5):576–8.
39. World Health Organization. HIV-associated tuberculosis. https://www.who.int/tb/areas-of-work/tb-hiv/tbhiv_factsheet.pdf?ua=1. Accessed 10 July 2020.
40. Johansen IS, Nielsen SL, Hove M, Kehrer M, Shakar S, Wøyen AV, Andersen PH, Bjerrum S, Wejse C, Andersen ÅB. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. Clin Infect Dis. 2015;61(4):554–62.
41. Shu CC, Wang JY, Yu CJ, Lee LN. Mycobacterial arthritis of large joints. AnnRheum Dis. 2009;68(9):1504–5.
42. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, O'Brien R, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS, Sotgiu G, Starke JR, Migliori GB, Vernon A. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):e147–95.