Rheumatic and Infectious Causes of Knee Pain

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Rheumatic Knee Pain

This chapter will focus on some of the more common autoimmune and autoinflammatory conditions which can cause knee pathology. Autoimmune diseases result from abnormalities of the adaptive immune system and usually involve the generation of autoantibodies. Examples of autoimmune disease include rheumatoid arthritis and systemic lupus erythematosus (SLE). Autoinflammatory diseases result from abnormalities of the innate immune system and include disorders like Adult-onset Still's disease and familial Mediterranean fever.

Autoimmune or autoinflammatory causes for knee pain should be considered in the differential diagnosis of knee pain particularly if there is evidence of inflammatory arthritis. Inflammatory arthritis is characterized by synovitis with warmth,

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swelling, pain, and reduced range of motion. A joint effusion may also be present, often in the suprapatellar region. Patients may also report prolonged stiffness with inactivity or upon awakening that improves with physical activity. This is in contrast to the symptoms often reported in patients with osteoarthritis with relatively short periods of stiffness and pain which worsens with physical activity.

Knee joint involvement in autoimmune or autoinflammatory disease can present as monoarticular arthritis or in the context of polyarticular arthritis. Extra-articular structures around the knee joint may also be affected. Many of the autoimmune and autoinflammatory diseases are systemic, warranting a comprehensive approach to history, and physical examination. Extensive serologic testing may be tempting when considering these disorders, but this approach is costly and can easily lead to confusing results, further clouding the clinical picture. It is best to use the history and physical examination to hone a differential diagnosis and consider serologic testing if a specific diagnosis is suspected.

History

When considering autoimmune or autoinflammatory etiologies of knee pain, one should tailor their history and examination to evaluate for evidence of a systemic autoimmune or autoinflammatory process in addition to the typically taken history (Table 9.1).

Additionally, pay particular attention to a family history of autoimmune or autoinflammatory disease, especially among first degree relatives.

Crystalline Arthropathies

Crystals can deposit in and around joint tissues, and the resulting immune response to these crystals may lead to inflammatory arthritis. The mere presence of crystals does not always equate to

Table 9.1 History and examination key points in evaluating for rheumatic diseases

Constitutional	Changes in weight, particularly unintentional weight loss which may signal an underlying inflammatory process. Recurrent fevers often reflect systemic inflammation and can be a symptom of infectious or rheumatic disease
Ocular	Assess for symptoms or a history of episodic eye redness associated with pain, photophobia or vision changes. These features may suggest a history of uveitis or scleritis
Ear, nose, throat (ENT)	A history of episodic swelling, redness, and pain of the ears or nose may suggest relapsing polychondritis or granulomatosis with polyangiitis (GPA). Recurrent epistaxis or nasal perforation can also suggest GPA. A history of oral and/or nasal ulcers can be symptoms of systemic lupus erythematosus (SLE) or systemic vasculitis
Cardiovascular	Chest pain with pleuritic features may be a sign of serositis. Chest pain which worsens with supine positioning which improves with seated position is classically a feature of pericarditis which can be a component of numerous rheumatic diseases including SLE, vasculitis and rheumatoid arthritis
Respiratory	Symptoms of new onset dyspnea with exertion or rest. Also querying about hemoptysis, which may be a symptom of systemic vasculitis
Gastrointestinal (GI)	If considering inflammatory bowel disease (IBD) associated arthritis or reactive arthritis, a GI review of systems is essential. Assess for symptoms or a history of recurrent abdominal pain, nausea, vomiting, diarrhea, melena and hematochezia
Genitourinary (GU)	Assess for symptoms or a history of genital ulcers or recent GU infection. Genital ulcers in the setting of knee inflammatory arthritis may suggest Behçet's disease. Knee inflammatory arthritis in the setting of a recent GU infection suggests reactive arthritis or gonococcal arthritis
Neurologic	Assess for symptoms or a history of sensory and/or motor neuropathy. For example, mononeuritis multiplex in the setting if knee inflammatory arthritis would suggest a systemic vasculitis

(continued)

Table 9.1 (continued)

Vascular	Assess for Raynaud's phenomenon which can be associated with a variety of rheumatic diseases
Musculoskeletal	Assess for pain or swelling of other joints beyond the knee. This includes asking about back pain. Inflammatory back pain is classically characterized by pain that is worse with inactivity, worse at night, and improves with physical activity
Integumentary	Assess for a history of skin rash, including those that are photosensitive, or skin ulcers. Many rheumatic diseases present with articular and skin involvement including psoriatic arthritis, reactive arthritis, adult-onset Still's disease, sarcoidosis, SLE, and systemic vasculitis

active inflammatory arthritis. The most common crystals which deposit in joints are monosodium urate (MSU) and calcium pyrophosphate. Other crystals include hydroxyapatite and calcium oxalate. The presence of crystals in synovial fluid does not rule out infection, and gout/pseudogout may present concurrently with septic arthritis. Conversely, acute crystalline arthropathy alone may present with fever and leukocytosis, mimicking infection. This underscores the importance of arthrocentesis and synovial fluid analysis.

Gout

Gout is the most common cause of crystalline arthropathy and commonly affects the knee in addition to other joints including the first metatarsophalangeal joint and ankle. Gout is caused by long-standing hyperuricemia which leads to deposition of MSU crystals. Crystal deposits may eventually form tophi and can progress to chronic, erosive arthritis. Acute gout may be triggered by a variety of etiologies including infection, trauma, sur-

gery, and stress including hospitalization. Medications including hydrochlorothiazide, loop diuretics, calcineurin inhibitors, angiotensin converting enzyme inhibitors, and pyrazinamide may lead to hyperuricemia. Other factors include consumption of purine-rich foods including red meat, seafood, beer, and other alcoholic beverages are also associated with hyperuricemia.

Clinical Presentation Gout frequently presents with acute onset joint pain with associated warmth, swelling, and decreased range of motion. Pain from acute crystalline arthropathy can be excruciating and patients will frequently complain of discomfort even with light palpation of the affected joint. When the knee is affected, a suprapatellar joint effusion is often present. Collections of uric acid precipitate, known as tophi, may be present in patients with long-standing, untreated gout. Tophi manifest as subcutaneous nodules that can be found around the knee, but are also commonly found on the medial aspect of the first MTP, extensor surfaces or even the pinna [1].

Diagnostic Studies Gout is diagnosed with arthrocentesis which often demonstrates inflammatory synovial fluid with white blood cell counts frequently exceeding 50,000/μL. Occasionally, white blood cell counts may be greater than 100,000/μL, mimicking septic arthritis, but gram stain will show no organisms and fluid culture will be negative. MSU crystals can be identified as needle-shaped, negative birefringent crystals under polarized light microscopy. Visualization of MSU crystals within neutrophils signifies acute gout. Serum urate levels can be checked, but may be normal during an acute gout attack. A high serum urate level may be helpful in establishing a history of hyperuricemia, but a normal or even low serum urate level does not rule out acute gout. Inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are typically elevated in acute gout.

Imaging Radiographs of the knee may show a joint effusion, tophi, or erosions with overhanging edges sometimes referred to as "rat bite" lesions [2].

Treatment Treatment of gout depends on whether the presentation is acute or chronic and if one or multiple joints are affected. For acute monoarticular gout of the knee, arthrocentesis can be both diagnostic and therapeutic. Intra-articular glucocorticoid injection, usually with triamcinolone or methylprednisolone, is very effective, but it is important to rule out infection before this is done. Other treatment options include a course of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, systemic glucocorticoids, or anakinra. Systemic glucocorticoids or anakinra are generally reserved for polyarticular flares. Treatment is often dictated by the patient's comorbidities, including diabetes, renal impairment or recent surgery, and current medications.

Long-term management of gout consists of urate-lowering therapy with the goal of reduced number of flares and progression of erosive disease. Commonly used medications include the xanthine oxidase inhibitors like allopurinol or febuxostat, and uricosuric agents such as probenecid. Pegloticase, a recombinant uricase enzyme, may be indicated in refractory cases of gout. These medications can paradoxically be associated with increased risk of gout flare within the first 3–6 months of initiating therapy. As such, low-dose colchicine, low-dose prednisone or NSAIDs are commonly prescribed during this period to mitigate flare risk [3].

Return to Activity There are no specific recommendations regarding return to activity, so return is based on level of pain and the patient's ability to tolerate physical activity. There is growing evidence that exercise is beneficial and may have anti-inflammatory properties in gout and other rheumatic diseases [4].

Calcium Pyrophosphate Deposition Disease (CPPD)

Acute calcium pyrophosphate deposition disease (CPPD) is also known as pseudogout. CPPD arthropathy is most often seen in older adults over the age of 60, and age is considered a risk factor for the development of the disease. Other risk factors include hemochromatosis, hypomagnesemia, and hyperparathyroidism. These etiologies should be considered particularly in patients with CPPD who are less than 60 years of age [5].

Clinical Presentation CPPD presents similarly to gout with severe pain, swelling, and limited range of motion. A moderate to large joint effusion may be present. The knee joint is the most commonly affected. CPPD is often associated with osteoarthritis and chondrocalcinosis, the deposition of calcium pyrophosphate in cartilage. CPPD may also present as a chronic inflammatory polyarthritis which can mimic rheumatoid arthritis.

Diagnostic Studies As with gout, synovial fluid analysis is usually inflammatory with white blood cell count ranging from 5000 to 100,000/μl. The presence of intracellular rhomboid shaped, positively birefringent crystals under polarized light is diagnostic for CPPD arthropathy. Patients can have both gout and CPPD concurrently, indicated by the presence of intracellular MSU and calcium pyrophosphate crystals in synovial fluid. Testing serum magnesium, parathyroid hormone, and iron studies should be particularly considered in patients with CPPD who are less than 60 years of age. ESR and CRP are usually elevated.

Imaging Radiographs of the knee showing chondrocalcinosis of the knee cartilage can be a clue that CPPD is present. However, chondrocalcinosis may be found incidentally on radiographs without overt CPPD. Isolated patellofemoral joint space narrowing is also a common, unique feature of knee CPPD [2].

Treatment Acute CPPD is treated much like acute gouty arthritis with either NSAIDs, colchicine or glucocorticoids. If the knee is the only joint affected, glucocorticoid injection can be considered. Treatment options for chronic CPPD can include colchicine or hydroxychloroquine [6].

Return to Activity As with gout, there are no specific recommendations regarding return to activity. Return is based on the level of pain and the patient's ability to tolerate physical activity.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) typically presents as an erosive, inflammatory polyarthritis, but oligoarthritis or monoarthritis may occur as well. RA most frequently affects the metacarpophalangeal and proximal interphalangeal joints of the hands, the feet, and yv wrists, but large joints like the knee are also commonly affected [7]. RA usually develops with a gradually increasing number of involved joints over a period of weeks to months.

Clinical Presentation Rarely, monoarthritis of the knee may be the presenting feature of RA. In this setting, the knee can be acutely inflamed with warmth, swelling, tenderness to palpation, and reduced range of motion. A joint effusion may be present in this case along with synovial thickening. Conversely, an acutely swollen knee in a patient with known rheumatoid arthritis with otherwise well-controlled disease should raise suspicion for septic arthritis. Patients with long-standing, uncontrolled RA may develop flexion contractures at the knee and valgus deformity. Other physical exam features may be boutonniere or swan neck deformities of the fingers, deformities of the toes including hammertoes, and subcutaneous nodules on the extensor surfaces known as rheumatoid nodules.

Diagnostic Studies Common laboratory features of active rheumatoid arthritis include elevated inflammatory markers, anemia of chronic disease, and thrombocytosis. Serology may be positive

for rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides8 (anti-CCP). Antinuclear antibodies may also be present. It is important to recognize that RF and anti-CCP are absent in a significant subset of patients, termed seronegative rheumatoid arthritis. Seropositive RA tends to be more severe and have more extra-articular manifestations including interstitial lung disease, scleritis, and rheumatoid vasculitis [8].

Imaging Radiographs of an affected knee in rheumatoid arthritis may demonstrate a joint effusion. Other common radiographic features include periarticular osteopenia, erosions, and symmetric joint space narrowing, particularly in long-standing and untreated disease [2].

Treatment Treatment of knee involvement in rheumatoid arthritis is generally managed in a similar fashion to RA affecting other joints. If infection has been ruled out, corticosteroid injection into an acutely swollen knee can provide significant pain relief. Systemic steroids may be warranted for a polyarticular RA flare. Methotrexate is the cornerstone of long-term management of rheumatoid arthritis as a conventional synthetic disease-modifying antirheumatic drug (csDMARD). Other csDMARDs including leflunomide, hydroxychloroquine, and sulfasalazine are options, the latter two of which may be combined with methotrexate. If moderate to high doses of methotrexate are unable to adequately control disease activity, biologic DMARDs (Table 9.2) or targeted synthetic DMARDs are considered in addition to methotrexate. Patients with end-stage joint damage of the knee from RA should be evaluated for joint replacement [7].

Return to Activity Physical activity and exercise is encouraged in patients with rheumatoid arthritis, and are associated with lower disease activity and pain scores. This applies to aerobic exercise, resistance training, and a combination of the two [9]. As with other rheumatic diseases, rheumatoid arthritis patients have an increased risk of cardiovascular disease. Exercise may help to mitigate this risk. Patients with damage and secondary osteoarthritis from RA benefit from targeted physical therapy to address

Table 9.2 Biologic DMARDs used in rheumatoid arthritis

Biologic DMARDs used in rheumatoid arthritis
Anti-tumor necrosis factor-α inhibitors (adalimumab, infliximab, etanercept, certolizumab pegol, golimumab)
IL-6 inhibitors (tocilizumab, sarilumab)
Rituximab: Binds to CD20 leading to B lymphocyte depletion
IL-1 receptor antagonist (anakinra)
Abatacept: CTLA-4 IgG, interferes with T cell co-stimulation
Targeted synthetic DMARDs
Janus kinase inhibitors (tofacitinib, baricitinib, upadacitinib)

specific muscle strength imbalances. Unfortunately, many rheumatoid arthritis patients are physically inactive, underscoring the importance of physicians discussing its benefits and encouraging patients to exercise.

Systemic Lupus Erythematosus (SLE)

Arthralgia is the most common musculoskeletal manifestation of SLE [10]. While tendonitis and tenosynovitis are common in SLE, true tendon rupture such as at the infrapatellar tendon is unusual [11]. When inflammatory arthritis is present, it is usually polyarticular and may involve the knee joint. Unlike rheumatoid arthritis, SLE usually causes non-erosive inflammatory arthritis. However, there is a subset of SLE patients whose joint disease behaves like rheumatoid arthritis and leads to significant erosions and joint deformities. These patients often have positive anti-CCP antibodies and are considered to be a lupus-rheumatoid arthritis overlap sometimes referred to as "rhupus" [12]. Arthralgia and arthritis can also be features of drug-induced lupus. Common drugs associated with drug-induced lupus include hydralazine, procainamide, isoniazid, and minocycline. TNF-α inhibitors have also been associated with drug-induced lupus [13].

Clinical Presentation In a lupus patient with knee pain, physical examination may simply demonstrate joint line tenderness to palpation. If inflammatory arthritis is present, the knee will be warm,

tender to palpation, have reduced range of motion, and often swelling with joint effusion. Poorly localized extra-articular pain, particularly if associated with pain in other body regions, may indicate myofascial pain from fibromyalgia which commonly occurs with SLE.

SLE can have a wide array of clinical manifestations with varying severity. Some specific extra-articular manifestations that can help aid in the diagnosis include skin rash, oral ulcers, nasal ulcers, serositis, nephritis, cytopenias, and secondary antiphospholipid antibody syndrome. SLE patients are also at risk of developing avascular necrosis, particularly due to chronic steroid use. The femoral heads are most commonly affected, but other sites like the distal femur may be affected as well [10].

Diagnostic Studies Laboratory testing in patients with SLE may show cytopenias including leukopenia, lymphopenia, anemia, and thrombocytopenia. Elevated serum creatinine, proteinuria, and hematuria may signal underlying lupus nephritis.

Serology in SLE almost always includes a positive antinuclear antibody (ANA). Other antibodies that may be seen include anti-Smith, anti-double stranded DNA, ribonuclear protein (RNP), anti-Ro, and anti-La. Low serum C3 and C4 complement levels are also common, and may be a sign of active disease if they are lower than a patient's established baseline. Rising double stranded DNA antibody titers can also be a sign of active disease, particularly lupus nephritis [10]. Thus, it is common for an SLE patient's rheumatologist to routinely monitor double stranded DNA antibody, C3 and C4 levels. Titers of other antibodies, including ANA, do not correlate with SLE disease activity and thus do not need to be repeated if they have been previously tested. Abnormal coagulation studies, especially a prolonged activated partial thromboplastin time, may signal the presence of a lupus anticoagulant and should prompt a workup for antiphospholipid antibody syndrome.

Anti-histone antibodies are seen in the majority of drug-induced lupus cases, but are not specific for the diagnosis as they can be seen in patients with SLE as well [13].

Treatment Treatment of SLE depends upon which clinical manifestations are present and their severity. Hydroxychloroquine is standard background therapy for nearly all SLE patients, and can be used for mild SLE-associated arthritis. Monoarthritis of a joint like the knee is amenable to steroid injection. For more severe polyarticular disease, methotrexate, azathioprine, or mycophenolate mofetil can be efficacious. If response to methotrexate is inadequate, addition of biologics such as belimumab or rituximab may be considered [14].

Return to Activities There are no specific recommendations regarding exercise modifications or return to activity in patients with SLE. Therapeutic exercise programs have not been found to worsen disease activity in SLE and instead may help improve levels of fatigue and depression [15].

Spondyloarthropathies

Spondyloarthritis (SpA) is categorized into inflammatory bowel disease (IBD)-associated SpA, psoriatic arthritis (PsA), reactive arthritis (ReA), and axial spondyloarthritis (AxSpA). While these are considered distinct disorders, the spondyloarthropathies can have phenotypic overlap.

Clinical Presentation All forms of SpA present with inflammatory arthritis. SpA may also present with enthesitis, inflammation of the tendinous insertion onto bone, which usually presents with swelling and/or tenderness over the entheses. Commonly affected areas include the plantar fascia, patellar, and Achilles tendon insertions [16]. Infrapatellar enthesitis presents with tenderness to palpation at the tibial tubercle. Localized swelling may also be present. Dactylitis, swelling of an entire digit, may also occur with any form of SpA. The presence of either enthesitis or dactylitis can help distinguish SpA from other causes of inflammatory arthritis like RA or SLE.

Diagnostic Studies Inflammatory markers like erythrocyte sedimentation rate and C-reactive protein are usually elevated in SpA, but normal levels do not rule out these diagnoses. Unlike many other autoimmune diseases, autoantibodies are typically absent in the spondyloarthropathies. The presence of HLA-B27 is associated with the spondyloarthropathies with AxSpA having the highest association [17]. However, HLA-B27 positivity is not a prerequisite for the diagnosis of SpA.

Imaging Radiographs of the knee in all forms of SpA may show symmetrical joint space narrowing, erosions, and joint effusion which reflect inflammatory arthritis. Bony proliferation or periostitis is a common radiographic feature of SpA. It may occur next to areas of erosion, along the bone shaft, across joints and at entheses [2]. This may be seen in the lateral view with bony proliferation at the superior and inferior surfaces of the patella.

Return to Activity No specific recommendations exist regarding return to activity for the various forms of SpA. In general, during acute manifestation of disease, weight bearing is as tolerated and as symptoms resolve, activities can progress. The European League Against Rheumatism (EULAR) guidelines strongly recommend the promotion of regular physical activity including aerobic activity, muscle strength, flexibility, and neuromotor performance for patients with osteoarthritis, rheumatoid arthritis, and spondyloarthritis [18].

Inflammatory Bowel Disease-Associated Spondyloarthritis

Clinical Presentation Inflammatory bowel disease (IBD)-associated spondyloarthritis (SpA) is a common extraintestinal manifestation of IBD. It is seen with Crohn's disease, ulcerative colitis, and microscopic colitis. IBD-associated arthritis may

present as peripheral SpA, sacroiliitis, axial SpA or a combination of the three. The knee is one of the most commonly affected joints [19]. While most IBD-associated SpA develops after IBD diagnosis, a significant proportion of patients may develop joint disease before intestinal manifestations. IBD-associated peripheral SpA is typically categorized into one of two types.

Type I peripheral SpA: often an oligoarticular arthritis which tends to occur early in the disease course of IBD. Like other extraintestinal manifestations of IBD, type I parallels bowel disease activity. This form is non-erosive, usually resolves within several months and does not typically require immunosuppressive therapy.

Type II peripheral SpA: Less common than Type I. This form of IBD-associated arthritis is most commonly polyarticular and affects the small joints of the hands although the knee joints may be involved as well. Type II is a chronic, erosive inflammatory arthritis that progresses independently of bowel disease activity. Immunosuppression is usually needed [19].

IBD-associated SpA should be considered in any patient with a known history of IBD who presents with knee pain. If inflammatory arthritis of the knee is present, the knee will be warm, tender to palpation with reduced range of motion. Swelling with joint effusion may be present. Localized tenderness or swelling at the tibial tubercle may indicate enthesitis. If IBD is present, patients will frequently complain of recurrent abdominal pain. They may also have varying degrees of diarrhea and hematochezia. Crohn's disease patients may develop oral ulcers and anal fissures. Fistula formation may also occur.

Diagnostic Studies Laboratory abnormalities in IBD-associated SpA may include elevated inflammatory markers like ESR and CRP. Anemia may reflect iron deficiency or chronic inflammation. Crohn's disease patients with small intestinal involvement may have features of malabsorption. As mentioned previously,

knee radiographs may show symmetrical joint space narrowing, erosions, periostitis, and joint effusion.

Treatment Many of the treatments used for IBD are effective for peripheral SpA, including sulfasalazine, methotrexate, and TNF-alpha inhibitors with the exception of etanercept. When considering treatment for IBD-associated SpA, it is important to identify the presence of peripheral SpA, axial SpA, or both, as certain medications which are effective for peripheral SpA may be ineffective for axial SpA. For example, sulfasalazine and methotrexate are effective for peripheral SpA but ineffective for axial disease. Vedolizumab, which is effective for bowel disease, is not effective for either peripheral or axial SpA. Conversely, the IL-17 inhibitors secukinumab and ixekizumab are effective for SpA but ineffective for IBD [20].

Reactive Arthritis

Reactive arthritis (ReA) is characterized by inflammatory monoarticular or oligoarticular arthritis that occurs within days to weeks of a recent infection, usually gastrointestinal or urogenital. *Chlamydia trachomatis* causing urethritis in men and cervicitis in women is one of the most commonly-associated pathogens with ReA. Causes of gastrointestinal infections with associated ReA include *Salmonella* and *Shigella* species, *Campylobacter jejuni*, and *Yersinia* species. More recently infections of other organisms including *Clostridiodes difficile* and *Chlamydia pneumoniae* have been recognized [21].

Clinical Presentation ReA primarily affects large joints of the lower extremities, with the knee being the most commonly involved [22]. If inflammatory arthritis of the knee is present, the knee will be warm, tender to palpation, and with reduced range of motion. Swelling with joint effusion may be present. Enthesitis is a common feature of ReA and may manifest as

patellar tendinopathy as described previously. ReA can have extra-articular manifestations as well. Ocular manifestations include conjunctivitis and uveitis. Cutaneous manifestations like keratoderma blennorrhagicum or circinate balanitis may occur. Historically the triad of arthritis, conjunctivitis and urethritis was referred to as Reiter syndrome, but this term has fallen out of favor.

Diagnostic Studies HLA-B27 is positive in up to 50–80% of patients with ReA, but is not a prerequisite for the diagnosis. Patients who have HLA-B27 appear to be at increased risk for a more severe disease course, are more likely to have axial involvement and have extra-articular manifestations [22].

Treatment Reactive arthritis is usually self-limited, resolving within several months. NSAIDs are considered a first line treatment. Monoarticular involvement of a lower extremity joint like the knee may be managed with intra-articular steroid injection. A short course of systemic glucocorticoids may be warranted for oligoarticular or polyarticular disease. Some patients may develop a chronic disease course lasting greater than 6 months. In these cases, consideration may be given to conventional synthetic DMARDs like sulfasalazine or methotrexate, although these medications are not effective for enthesitis or dactylitis. If these therapies are ineffective, TNF-alpha inhibitors may be considered. Research studies have evaluated whether a prolonged course of antibiotics is beneficial in patients with *Chlamydia*-associated ReA, but with mixed results [22].

Psoriatic Arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Estimates in the literature report PsA occurs in up to 30% of patients with psoriasis [23]. The knee may be affected in PsA, but is not the most commonly affected joint. PsA has historically been categorized into one of five subtypes [24].

1. Asymmetric oligoarticular arthritis: Knee and ankle joints may be involved, but most commonly affects the distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), and metatarsophalangeal (MTP) joints.
2. Predominant DIP involvement.
3. Polyarticular: can resemble rheumatoid arthritis in its distribution affecting the PIPs, MCPs, and wrists.
4. Arthritis mutilans: Variant with severe erosions and joint deformities with telescoping of digits.
5. Isolated axial spondyloarthritis: sacroiliac and vertebral involvement. Classically, sacroiliac involvement in PsA is unilateral.

Psoriasis develops about 10 years before the onset of inflammatory arthritis in about 70% of cases. Roughly 15% of patients will develop psoriasis and inflammatory arthritis together. This group of patients will often experience simultaneous flares of their skin and articular disease [23].

If inflammatory arthritis of the knee is present, the knee will be warm, tender to palpation with reduced range of motion. Swelling with joint effusion may be present. As with other forms of SpA, enthesitis is a common feature. When considering PsA in the differential diagnosis for inflammatory arthritis of the knee, it is important to both query and closely examine the patient for the presence of psoriatic plaques or nail changes. Psoriasis does commonly affect the skin over extensor surfaces, but small plaques may only affect skin behind the ears, the intertriginous regions of the groin, or gluteal cleft. At the groin site, lesions may appear as plaques without scale, sometimes called inverse psoriasis.

Diagnostic Studies Laboratory studies may show elevated ESR and CRP, but these are non-specific findings. HLA-B27 may be positive but is not a prerequisite for diagnosis.

Imaging Radiographic findings of the knee may show symmetric joint space narrowing with marginal erosions with adjacent bony proliferation, and additional bony resorption [2]. X-rays may also show periostitis and bony spurs at areas of enthesitis.

Table 9.3 Treatments for psoriatic arthritis

Conventional synthetic DMARDs for PsA
NSAIDs
Methotrexate
Leflunomide
Sulfasalazine
Glucocorticoids
Intra-articular steroids can be beneficial for patients with knee inflammatory arthritis due to PsA
Systemic steroids may be considered in severe disease, but there is a chance of significant worsening of skin disease if steroids are withdrawn
Biologic DMARDs for PsA
Anti-tumor necrosis factor-α inhibitors (adalimumab, infliximab, etanercept, certolizumab pegol, golimumab)
IL-12/23 inhibitor (ustekimumab)
IL-17 inhibitors (ixekizumab, secukimumab)
IL-23 inhibitors (guselkumab is FDA approved for PsA)
Abatacept: CTLA-4 IgG, interferes with T cell co-stimulation
Targeted synthetic DMARDs for PsA
JAK inhibitors: Tofacitinib is approved for PsA
Phosphodiesterase (PDE) 4 inhibitor (apremilast)

Treatment There are numerous treatments available for PsA, many of which are also effective for skin disease [25] (Table 9.3).

Axial Spondyloarthritis

As the name implies, axial spondyloarthritis (AxSpA) primarily affects the spine and bilateral sacroiliac joints, but may have a peripheral component. Ankylosing spondylitis refers to axial SpA with radiographic evidence of disease, which differs from non-radiographic AxSpA in which spondyloarthritis or sacroiliitis may only be visible on magnetic resonance imaging [17].

Clinical Presentation As with other forms of SpA, knee involvement in AxSpa often presents as inflammatory arthritis. Enthesitis of the patellar tendon may be present, manifesting as tenderness over the tibial tubercle sometimes with localized swelling.

Treatment csDMARDs like methotrexate, leflunomide, and sulfasalazine, which are effective for peripheral SpA, are ineffective for axial disease. In this case, NSAIDs are considered the first line disease-modifying agents, however they are often inadequate to control disease. With both axial and peripheral SpA (of the knee, for instance), consideration must be given to medications which will have activity for both. Biologic DMARD classes which are effective for axSpA include anti-TNFα inhibitors and IL-17 inhibitors. Research is ongoing regarding the efficacy of JAK inhibitors in AxSpA. Systemic glucocorticoids are considered ineffective for AxSpA and generally should not be used.

Return to Activities Physical activity and exercise are essential components in the management of AxSpA. Many of the current recommendations focus on spinal mobility, and no specific recommendations exist regarding return to activity with regard to knee joint involvement. Generally, most exercise modalities are safe in patients with ankylosing spondylitis. However, in patients with advanced disease, balance or mobility issues, osteoporosis, or have cardiac and pulmonary complications, certain forms of exercise may be contraindicated. These exercises include high impact exercise such as contact sports and certain forms of martial arts, high velocity or strongly resisted exercise, particularly if truncal flexion or rotation is involved, exercise that excessively challenges posture, balance or cardiorespiratory function, or exercises which excessively challenge mobility of a specific joint which is affected by ankylosis [26].

Sarcoidosis

Sarcoidosis is an inflammatory disease that is histologically characterized by non-caseating granuloma formation in tissues. Sarcoidosis most commonly affects the lungs with manifestations including hilar lymphadenopathy and parenchymal disease. Other commonly affected organs include the eye, often manifesting as uveitis, and skin, but essentially any organ can be affected. Musculoskeletal involvement occurs in about 25–30% of sarcoid-

osis and may manifest as inflammatory arthritis, inflammatory tenosynovitis or periarticular inflammation [27].

Clinical Presentation Inflammatory arthritis in sarcoidosis has either an acute or chronic presentation. Acute sarcoid arthritis usually affects large joints of the lower extremities, particularly the ankles, but the knee is also commonly involved. It is typically an oligoarthritis, but monoarthritis can occur [28, 29]. If inflammatory arthritis of the knee is present, the joint will be warm, tender to palpation, and with reduced range of motion. Swelling with joint effusion may be present. Swelling and pain with intact range of motion is more suggestive of periarticular inflammation [30]. Acute arthritis may be a part of Lofgren's syndrome which comprises bilateral hilar lymphadenopathy, arthralgia/arthritis, and erythema nodosum. The majority of cases of Lofgren's syndrome resolve spontaneously. Chronic sarcoid arthropathy has varied presentations but may present as symmetrical oligoarthritis. Sarcoidosis tends to declare its organ involvement within the first 3–5 years of the disease. After that, it is uncommon for new organ involvement to occur [29].

Diagnostic Studies Serum angiotensin converting enzyme (ACE) and lysozyme levels are often checked to evaluate for sarcoidosis. Either or both may be elevated in sarcoidosis, however neither is sensitive nor specific [29]. Additionally, both ACE and lysozyme do not correlate with disease activity. Hypercalcemia and hypercalciuria may be present, reflecting increased 1,25-dihydroxy-vitamin D levels. Rheumatoid factor can be positive in sarcoidosis as well. If a diagnosis of sarcoidosis is being considered, a chest radiograph should be obtained to evaluate for evidence of hilar lymphadenopathy or pulmonary parenchymal disease. Except in cases with classical presentation like Lofgren's syndrome for example, tissue biopsy is usually needed for diagnosis. A biopsy showing non-caseating granulomas in the appropriate clinical setting is diagnostic.

Treatment First line treatment for most manifestations of sarcoidosis is low to moderate dose glucocorticoids. Lofgren's syndrome can often be managed with NSAIDs. However, if the patient continues to be symptomatic or has a contraindication to NSAIDs,

low to moderate dose glucocorticoids may be used. In patients whose disease is either refractory to steroids, or in situations where steroids cannot be tapered due to persistent disease activity, steroid sparing agents like methotrexate and azathioprine may be considered. Anti-TNF-α inhibitors, particularly infliximab and adalimumab, may be considered in refractory sarcoidosis [29].

Return to Activities There are no limitations of range of motion or activity in musculoskeletal involvement in sarcoidosis. Weight bearing and activity should be encouraged as tolerated.

Sjögren's Syndrome

Sjögren's syndrome (SjS) is an autoimmune sicca syndrome characterized by inflammatory infiltration of exocrine glands. It may be primary or secondary in the setting of other autoimmune diseases like rheumatoid arthritis or SLE. SjS can have numerous extraglandular manifestations.

Clinical Presentation Musculoskeletal involvement can include arthralgias as well as non-erosive inflammatory arthritis, both of which can involve the knee. Joint symptoms are usually polyarticular [31]. When inflammatory arthritis of the knee is present, there is usually tenderness to palpation, warmth, swelling, and reduced range of motion. A joint effusion may be present. Generalized periarticular and myofascial pain may indicate underlying fibromyalgia which may occur with SjS.

Diagnostic Studies Laboratory features of SjS can include elevated inflammatory markers like ESR and CRP when the disease is active. Autoantibodies to Ro (SSA) and La (SSB) are usually positive in high titers, although they may be seen in other autoimmune disorders. Rheumatoid factor is commonly positive. A positive anti-CCP antibody is rare in primary SjS and its presence in a patient with known SjS should suggest underlying rheumatoid arthritis with secondary SjS.

Treatment Joint symptoms, particularly inflammatory arthritis, may be treated initially with hydroxychloroquine or methotrexate. Low-dose glucocorticoids may be used as well [31]. Monoarthritis of the knee is amenable to intra-articular glucocorticoid injection.

Return to Activity Weight bearing and activity is as tolerated.

Adult-Onset Still's Disease

Adult-onset Still's Disease (AOSD) is an autoinflammatory disorder that represents the adult-onset equivalent of systemic juvenile idiopathic arthritis.

Clinical Presentation AOSD is characterized by high daily fevers, evanescent pink rash, and arthralgias and arthritis. The rash classically appears with fever and abates as fever resolves. Between febrile episodes, patients appear and feel otherwise healthy. Other features may include hepatosplenomegaly, lymphadenopathy, and sore throat. Serositis, often manifesting as pericarditis sometimes with a pericardial effusion, is sometimes a feature. AOSD tends to follow one of three disease patterns [32]:

1. Monocyclic: Solitary episode occurs and then resolves completely with no further flares.
2. Polycyclic: Recurrent flares with periods of remission.
3. Chronic: Disease is persistently active.

Inflammatory arthritis is most associated with the chronic form of AOSD and typically affects the small joints of the hands but may also affect larger joints like the knee. Knee examination is consistent with findings of inflammatory arthritis including warmth, tenderness to palpation, range of motion reduction and potentially an effusion. If examined during a febrile episode, the patient may appear unwell, diaphoretic, and tachycardic. Erythematous to pink macules and patches may be present, particularly on the trunk and proximal extremities. The rash may resemble urticaria. A palpable liver or spleen may be present reflecting hepatosplenomegaly [32].

The most severe complication of AOSD is macrophage activation syndrome (MAS) which is a hyperinflammatory state characterized by persistent high fevers, extreme hyperferritinemia, cytopenias, and liver dysfunction with coagulopathy. Some similarities have been drawn to MAS and the hyperinflammatory state sometimes associated with severe SARS-CoV-2 infection (COVID-19). Unabating fevers in a patient with known AOSD should prompt consideration for developing MAS [33].

Diagnostic Studies Laboratory features of AOSD include a neutrophilic predominant leukocytosis, elevated serum ferritin, and elevated liver enzymes. Given that these laboratory features are not specific to AOSD, infection and malignancy need to be excluded.

Treatment Treatment includes oral glucocorticoids initially, usually at doses of 0.5–1 mg/kg/day, and tapered over weeks to months depending on clinical response [32]. Steroid sparing agents that have been demonstrated to be effective include methotrexate, anakinra, rilonacept, and canakinumab.

Return to Activities Patients will likely not feel well enough to exercise during febrile episodes, but may feel well enough to do so between episodes or when the disease is well-controlled or in remission. Weight bearing and activities are as tolerated.

Polymyalgia Rheumatica

Clinical Presentation Polymyalgia rheumatica (PMR) is an inflammatory disorder primarily characterized by pain and stiffness of the neck, shoulder girdle, and hip girdle. Patients may also report constitutional symptoms such as fever, malaise and fatigue. The symptoms of PMR are primarily due to periarticular inflammation, including bursitis. Peripheral inflammatory arthritis is a less common feature but when present, may affect the knees or wrists [34]. In this scenario the knee will be warm, tender to palpation and exhibit reduced range of motion. Knee pain without these features in a patient with PMR may indicate hip pathology.

PMR is associated with giant cell arteritis, and patients should be questioned about symptoms of recurrent fever, headache, jaw or tongue claudication, visual disturbances, and balance issues.

Diagnostic Studies Laboratory features of PMR typically include elevated ESR and CRP.

Treatment Symptoms of PMR respond rapidly to low-moderate dose glucocorticoids, the equivalent of prednisone 10–20 mg per day [34]. A lack of response to this therapy should prompt consideration of alternative diagnoses.

Return to activities Weight bearing and activities are as tolerated.

Other Causes of Knee Pain (Table 9.4)

Tenosynovial Giant Cell Tumor

Previously known as pigmented villonodular synovitis, tenosynovial giant cell tumor is a rare cause of knee pain. The vast majority of tumors are benign, although a small number of malignant tenosynovial giant cell tumors have been reported. The knee is the most commonly involved joint and usually presents as monoarticular arthritis. Within the knee itself, the tumor often affects the intercondylar region of the femur [35].

Clinical Presentation Symptoms include pain with reduced range of motion. Recurrent episodes of swelling may occur.

Diagnostic Studies If a joint effusion is present, synovial fluid analysis is classically bloody and non-inflammatory.

Radiographs of the knee may show periarticular cystic lesions. MRI is particularly helpful in this diagnosis and may show a soft tissue mass with hemosiderin deposits.

Table 9.4 Other causes of knee pain

Other autoinflammatory syndromes	Familial Mediterranean Fever, TNF-receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS)
Primary systemic vasculitis	• Large vessel vasculitis: Takayasu arteritis, giant cell arteritis • Medium vessel vasculitis: Polyarteritis nodosa, Kawasaki disease • Small vessel vasculitis: ANCA-associated vasculitis, cryoglobulinemic vasculitis, IgA vasculitis Mixed vessel size: Behçet's disease Inflammatory arthritis affecting the knee can be a manifestation of these disorders but is less prominent than many other distinguishing disease features
Mixed connective tissue disease	A specific overlap syndrome with varying features of lupus, systemic sclerosis and myositis associated with high titer anti-U1-RNP antibodies. Nearly all patients have Raynaud's phenomenon. Inflammatory arthritis is a common feature and can be erosive. Most commonly involved joints are MCPs, PIPs, MTPs but the knee joint may be involved as well.

Treatment Treatment may include total synovectomy with adjuvant radiation therapy [36]. Unfortunately, tumor recurrence may occur, particularly if there is residual synovium present after surgery.

Synovial Chondromatosis

Synovial chondromatosis is characterized by the formation of multiple nodules of hyaline cartilage in subsynovial connective tissue. Nodules may become calcified. The knee is affected in over 50% of cases [37]. Synovial chondromatosis is almost always benign, but may rarely develop into synovial chondrosarcoma [35].

Clinical Presentation Patients may present with knee pain, swelling, and with a locking or clicking sensation. Physical examination may reveal swelling, reduced range of motion, and crepitus.

Imaging Plain radiographs of the knee usually show multiple intra-articular, oval-shaped, calcified loose bodies.

Treatment Treatment of synovial chondromatosis involves synovial excision and removal of loose bodies [38].

Infectious Knee Pain

This section will cover common causes of infectious knee pain. Organisms that can infect a knee joint include bacteria, viruses, fungi, mycobacteria, with bacteria being the most common. The term septic arthritis encompasses joint infections of any of the above organisms. Early diagnosis is important as infection can lead to degradation of joint cartilage as early as 48 hours [39, 40].

Bacterial Arthritis

Specific Organisms and Population (Adults) [41]

- *Staphylococcus aureus* (*S. aureus*): general population, pre-existing joint disease, prosthesis, open skin or other infection. Most common overall.
- Coagulase-negative staphylococci: prosthetic joint infection.
- Streptococcal species (i.e.: *Streptococcus pneumoniae*): general population, splenic dysfunction.
- *Neisseria gonorrhoeae*: most common in sexually active general population.
- Aerobic gram-negative (i.e.: *Pseudomonas* species): immunocompromised, gastrointestinal infection.

- Anaerobic gram-negative: immunocompromised, gastrointestinal infection, human bite, decubitus ulcers, intra-abdominal abscess.
- Brucellosis: general population with animal exposure.
- *Borellia burgdorferi*: general population with exposure to ticks.
- *Mycoplasma*: immunocompromised.

Specific organisms (children): group B streptococci, group A streptococci (*streptococcus pyogenes, Kingella kingae*) gram-negative enteric bacilli, *S. aureus.*

Risk Factors Bacterial arthritis of the knee can be as a result of other infections that cause bacteremia and hematogenous seeding or direct inoculation of the joint. Risk factors that predispose a patient include pre-existing joint disease (including gout, CPPD or autoimmune diseases like rheumatoid arthritis), skin or soft tissue infection, recent joint surgery or injection, trauma, animal bite, advanced age, intravenous (IV) drug use, indwelling ports or catheter, and immunosuppression.

Clinical Presentation A patient with bacterial arthritis will typically present with acute (around one to five days) joint pain, swelling, redness, warmth, and stiffness, muscle spasm, with or without accompanied fever. Larger joints such as the knee are more often affected. Majority of the cases are monoarticular. Bacterial monoarthritis is more common, however, oligo- or polyarticular septic arthritis is more likely in patients with rheumatic or other systemic connective tissue disease [42].

Physical Exam Examination of the affected knee joint will demonstrate erythema, edema, warmth, diffuse tenderness to palpation. An effusion is palpable. Range of motion, both passive and active, is typically restricted and painful, which leads to dysfunctional ambulation and difficulty weight bearing.

Outside of the focused knee exam, evaluate all other joints to determine if polyarthritis is present. Evaluate for a source of infection such as open wounds or abscesses, indwelling ports or catheters. Examine cardiopulmonary systems. Vitals may show elevated temperature. Hypotension and tachycardia may be present in the setting of bacteremia and hematogenous seeding.

Diagnostic Studies Synovial fluid should be aspirated from the knee joint prior to administration of antibiotics. Analysis involves volume (typically >3.5 mL), gross appearance (cloudy, opaque, yellow, purulent), viscosity (variable), crystals (none), cell count and differential (WBC >50,000/μL, polymorphonuclear leukocytes >75%), gram stain (large number of neutrophils and organisms), and bacterial culture, including Neisseria gonorrhoeae culture (positive if bacterial). Certain bacterial organisms such as Neisseria may have lower WBC counts at >2000/μL. If the leukocyte count is >50,000/μL and mostly neutrophils, but a negative gram stain and culture, it is still presumed to be bacterial septic arthritis. Synovial fluid should be checked for crystals as crystal-induced disease can mimic bacterial septic arthritis clinically and can also occur concomitantly [43].

A CBC will likely show leukocytosis with left shift, however, this is non-specific. ESR and CRP may also be elevated, but is another non-specific finding. Blood and wound cultures should be obtained to determine the source of infection in hematogenous spread and for identification of pathogen [41].

Imaging Imaging is not required to diagnose bacterial septic arthritis but can be used in conjunction with synovial fluid analysis. Knee X-rays may show soft tissue swelling, joint space widening or narrowing, joint effusion, erosions, osteomyelitis, subcutaneous emphysema, foreign body, or trauma. Ultrasonography may show joint effusion, cortical irregularities, or separate fluid collection.

An echocardiogram may be necessary to evaluate for endocarditis especially in an IV drug user.

Treatment In order to appropriately diagnose bacterial septic arthritis, synovial fluid must be collected prior to administration of antibiotics. At the time of synovial fluid collection, the knee joint should be fully drained with large-bore needle aspiration with or without ultrasonography. Indications for arthroscopic or open surgical drainage and irrigation include persistent effusions despite serial aspirations, inadequate drainage via needle, loculated effusions, penetrating trauma, or retained foreign body. If the infection is severe, repeated aspiration or drainage may be required. If the aspiration and drainage is adequate, often the patient improves clinically and lab values return to normal [41].

Antibiotics When there is a high suspicion of bacterial septic arthritis, empiric antibiotics should be broad spectrum and cover the most likely pathogen based on age and risk factors.

If the gram stain shows gram-positive organism:

- Gram-positive cocci → empiric vancomycin.
- Methicillin-susceptible S. aureus (MSSA) → beta-lactam agent.
  - Examples: Cefazolin, nafcillin, oxacillin
  - If allergies to penicillins → vancomycin
- Methicillin-resistant S. aureus (MRSA) → vancomycin.
  - If allergy or intolerance → Daptomycin or linezolid or clindamycin

If the gram stain shows gram-negative organism:

- Gram-negative bacilli → cephalosporin.
- Ceftriaxone, cefotaxime, ceftazidime, cefepime
- Pseudomonas aeruginosa: initial empiric therapy with two anti-pseudomonal agents.
  - Cephalosporin + ciprofloxacin or aminoglycoside
  - If allergy to cephalosporin: Aztreonam 2 g IV every 8 h
- Negative initial Gram stain → vancomycin.

- If trauma, add a third-generation cephalosporin
- If immunocompromised and/or IV drug user, add anti-pseudomonal cephalosporin

In all instances, await susceptibility data and narrow antibiotic therapy for definitive treatment and to avoid antibiotic resistant bacteria.

The duration of antibiotic therapy should be tailored to each case. In general, uncomplicated cases typically require a shorter course of IV therapy (~7 days) with additional 14–21 day oral therapy. For bacterial septic arthritis with bacteremia, duration of IV therapy is at least 14 days and additional oral therapy for at least 14–21 days [41].

Return to Activities There is no indication for immobilization of the joint. Passive range of motion should be done to preserve mobility. Weight bearing can be avoided until signs of inflammation have decreased. In addition, comorbidities and the source of bacteria in bacterial septic arthritis contribute significantly to the outcome. Uncomplicated cases are likely to be discharged home with progressive therapy and return to regular function as tolerated. Those with pre-existing conditions or complicating factors may require discharge to a facility for rehabilitation and longer term stay. Return to baseline functional status in this case is slower and likely diminished. Complete antibiotic therapy and clearance of infection, stabilization of comorbidities, along with appropriate physical therapy is vital to recovery.

Gonococcal Arthritis

Neisseria gonorrhoeae can lead to disseminated gonococcal infection which can cause arthalgias or purulent arthritis, most commonly in sexually active young adults. There may be asymptomatic gonococcal mucosal colonization of genitourinary or pharyngeal systems that lead to bacteremia and disseminated gonococcal infection [40, 41, 44].

Risk Factors A sexually active population is most at risk. Women during menstruation and pregnancy and those who are immunocompromised (complement deficiency) can also be at increased risk.

Clinical Presentation Typical symptoms include migratory polyarthralgias, tenosynovitis, dermatitis, fever (all in combination is called arthritis-dermatitis syndrome), genitourinary symptoms, and purulent arthritis in one or more joints. Purulent arthritis typically involves knees, wrists, ankles.

Diagnostic Studies Diagnostic testing includes blood cultures, mucosal site specimen cultures, and synovial fluid analysis. The average synovial fluid leukocyte count for gonococcal arthralgia is lower at ≤20,000/μL. Because the arthralgia is as a result of immune response and immune-complex deposition, gram stain, synovial fluid cultures, and even blood cultures may return negative. If the joint has developed gonococcal purulent arthritis, the synovial fluid would show leukocytes >50,000/μL and a positive gram stain [43].

Treatment Initial treatment is with ceftriaxone (alternatively, cefotaxime or ceftizoxime) along with presumptive treatment for chlamydia with doxycycline or azithromycin. Depending on susceptibility data, treatment may be changed to fluoroquinolones or penicillin if purulent arthritis is not present. Purulent arthritis should be treated with ceftriaxone for at least 7–14 days along with aspiration or drainage. Those with penicillin allergies typically can use cephalosporins safely. Those with beta-lactam allergies should undergo desensitization [44].

Imaging X-rays are typically benign in polyarthralgias. In purulent arthritis, knee X-rays may show soft tissue swelling, joint space widening or narrowing, joint effusion, erosions, osteomyelitis, subcutaneous emphysema, foreign body, or trauma. Ultrasonography may show joint effusion, and cortical irregularities.

Return to Activities With appropriate antibiotic management, patients typically make a full recovery without residual deficit. There is no indication for immobilization of the joint and range of motion should be preserved passively and actively. With polyarthralgias, weight bearing is as tolerated. With purulent arthritis, weight bearing can be avoided until signs of inflammation are decreased. Return to activity is progressive and as tolerated.

Lyme Arthritis

Infection with the spirochete *Borrelia* leads to Lyme disease. *Borrelia burgdorferi* (*B. burgdorferi*) and *Borrelia mayonii* are the most common species in the United States. The bacteria is transmitted to humans through the *Ixodes* tick bite. Early localized disease has the characteristic erythema migrans (EM) skin lesion, with a central clearing and bulls-eye appearance. Early disseminated disease has multiple EM skin lesions occurring days to week after infection along with intermittent arthralgias and myalgias, and neurologic or cardiac findings that present weeks to months after infection. Late Lyme disease has associated mono- or oligoarthritis of large joints. The knee is a commonly affected joint. The arthritis can be migratory, intermittent, or persistent. Onset is variable and can present months or more after initial infection [40].

Clinical Presentation While technically Lyme arthritis is an infectious arthritis, the presentation is more akin to inflammatory arthritis since it creates an inflammatory synovial response. Fever is less common. The knee joint will have pain and swelling. Oftentimes, symptoms will wax and wane. If untreated, about 10% of patients will develop chronic inflammatory synovitis leading to erosions and destruction of the joint.

Despite months of treatment, a small portion of patients will develop post-infectious persistent Lyme arthritis. This arthritis is characterized by smaller knee joint effusions. A significant increase in synovial proliferation is likely associated with the recurrent effusions. The persistent arthritis can last several years [41].

Physical Exam Knee joint examination is overall less painful with range of motion and weight bearing. There may be pain along the joint lines along with a palpable effusion.

Diagnostic Studies Serological testing positive for serum immune globulin G (IgG) to *B. burgdorferi* is used to confirm the diagnosis of Lyme disease. Synovial fluid analysis of the joint fluid will portray an inflammatory arthritis. Fluid will be translucent to opaque, yellow in color, low viscosity, average WBC count 10,000–25,000/μL, polymorphonuclear leukocytes >50%. Synovial fluid culture is typically not positive. Imaging is not required for diagnosis [43].

Treatment Initial treatment starts with an oral antibiotic such as doxycycline or amoxicillin for 28 days. If prior treatment is ineffective or if there is persistent arthritis, IV ceftriaxone for 14–28 days or another 28 day course of oral antibiotics can be used. In post-infectious Lyme arthritis where both oral and IV antibiotic therapy is ineffective, consider management by a rheumatologist for DMARDs, or arthroscopic synovectomy. Overall, without treatment, post-infectious Lyme arthritis typically resolves spontaneously, though it may take a significant amount of time and the risk of damage to bone and cartilage increases.

Return to Activities Restrictions in persons with Lyme arthritis include decreasing high levels of activity and high impact activities while the knee joint inflammation is active. Rest followed by range of motion directed physical therapy can be helpful for quicker recovery.

Prosthetic Joint Septic Arthritis

There is a higher incidence of prosthetic knee joint infections over other joints such as the hip and shoulder. There is increased risk in those who have comorbidities such as diabetes, malignancy, rheumatic diseases, kidney disease, immunosuppression through

infection or medication, prior injection at the same joint, wound infections, and bacteremia. Organisms include *S. aureus*, coagulase-negative staphylococci, beta-hemolytic streptococci, gram-negative bacilli, enterococci, or anaerobes. Fungal and mycobacterial infections are also possible. The presence of hardware can lead to formation of biofilm and increases the risk of infection [45].

Clinical Presentation If infection is present less than 3 months after surgery, it is considered early onset, 3–12 months is considered delayed, and greater than 12 months after surgery is considered late onset. Early onset infection can present as pain, erythema, effusion, induration of incision, wound drainage or dehiscence, and fever and is usually as a result of implantation. It is also possible as a result of superficial wound spread. Delayed onset infection symptoms can be more subtle and often are attributed to failure or loosening of the prosthesis. Delayed onset of symptoms may be as a result of infection during implantation with less virulent organisms, including coagulase-negative staphylococci. There can be persistent joint pain in weight bearing and range of motion which can be attributed to hardware loosening instead of infection. In addition, fever and mild effusion may be present along with a sinus tract with drainage. Late onset is usually as a result of hematogenous seeding. Symptoms will be similar to early onset infection [46].

Diagnostic Testing Diagnosis via culture can be missed due to quality of swab or tissue culture, slow growing bacteria, antibiotic use prior to culture, or difficult to culture organisms due to lower virulence or media type. Positive culture with prominent organisms such as *S. aureus*, or a sinus tract that connects with the prosthesis is assumed to be true prosthetic joint infection. Two or more cultures positive for a less common or lower virulent organism can also be assumed to be true infection over contamination. Laboratory data is non-diagnostic with leukocytosis and elevated inflammatory markers such as ESR and CRP. X-ray of the joint can show soft tissue swelling, fracture, or lucency of bone sugges-

tive of hardware loosening but may be non-diagnostic in early onset infection. Other imaging modalities such as CT, MRI, or bone scans are not typically used for diagnosis. Arthrocentesis and synovial fluid analysis can be categorized as septic during early onset infection. However, in delayed and late onset infection, fluid leukocyte count can be much lower and have other fluid characteristics that fit both inflammatory and septic synovial fluid. Synovial fluid should be cultured. It is important for appropriate aseptic technique during aspiration to avoid contamination. Sinus tracts should be aspirated and drained and sent for culture. During removal of an infected prosthesis, multiple samples from different areas should be obtained for culture.

Treatment Antimicrobial treatment should be started after cultures are obtained and should be tailored to culture results and susceptibilities. Empirically, vancomycin in combination with a third- or fourth-generation cephalosporin can be used. Surgical options include debridement and removal of prosthesis with or without reimplantation, or amputation. The prosthesis can be retained, however, it is more common to explant the prosthesis, treat with antimicrobial therapy, and reimplant the prosthesis. Reimplantation should be delayed as recurrence of infection is common within several weeks to months. Without removal of the prosthesis, chronic antibiotic suppression may be required [47].

Return to Activity Patients are often non-weight bearing during acute stages of infection and also after explant of a prosthesis and/or amputation. Physical and occupational therapy is important to prevent muscle wasting and to preserve other joint mobility. As a result of the infection, patients may have some chronic pain in addition to limited use of the joint. Successful return to near-baseline activity is seen more with patients who explant and reimplant the prosthesis. Rehabilitation after reimplantation allows for immediate weight bearing as tolerated and progressive increase in activity over the course of weeks. The overall functional outcome may be diminished compared to those who did not have a prosthetic joint infection [48].

Viral Arthritis

Enterovirus (i.e.: coxsackie virus and echovirus) Overall, arthritis is rare in enterovirus infections. However, for non-specific viral arthritis, enterovirus is the most common. Enterovirus arthritis can affect both small and large joints, including the knee [49].

Clinical Presentation Joint symptoms such as generalized knee pain and stiffness are typically self-limited. Acute viral symptoms will likely be present, such as fatigue, fever, sore throat, rhinorrhea, cough, rash, and pleuritic chest pain.

Diagnostic Studies Non-specific laboratory findings may be present such as elevated ESR and leukocytosis. Aspiration of joint fluid may show 2000- > 10,000 WBC/'μL.

Treatment Supportive care.

Hepatitis A

Arthritis is rare. Knee arthralgias may occur. The infection is self-limited and treatment for the joint pain is supportive care [50].

Hepatitis B (HBV)

Knee or other joint pain can be the first manifestation of acute hepatitis B infection and occurs a few weeks before jaundice. The joint pain can be symmetric or migratory and typically signal the prodrome phase of infection. It is theorized that deposition of immune complexes into joints is what causes the arthritis.

Clinical Presentation Joint stiffness is present, particularly in the morning. Typically, fever, skin urticaria or a maculopapular rash will manifest along with the joint pain. Joint symptoms can last for days up to weeks. Joint symptoms can resolve at the time

jaundice develops. If arthralgias continue, they regress as jaundice regresses. Acute HBV joint arthritis is less likely to become chronic arthritis or cause permanent damage to the joint. However, if a person has a chronic HBV infection, joint arthritis can be prolonged and be more inflammatory in nature as seen in joint fluid analysis.

Treatment Supportive therapies for joint manifestation. Treat the HBV with supportive therapies or in the case of chronic HBV with antivirals such as interferon and nucleos(t)ide analogs [51].

Hepatitis C (HCV)

Acute HCV infection is more associated with arthralgias and myalgias. Chronic HCV infection can be associated with chronic arthralgias and arthritis.

Clinical presentation Chronic HCV arthritis is non-erosive and does not cause deformities. Presentation can be monoarticular, like the knee, or oligoarticular. Common complaints include joint pain and stiffness.

To distinguish hepatitis from other viral illnesses, laboratory values will show abnormal liver function tests, decrease in complement levels, increased circulating immune complexes, and positive specific hepatitis surface antigen (i.e.: HBsAg) [52].

Treatment Supportive care for the joint manifestations. Treat the HCV with appropriate antiviral medications [53].

Parvovirus B19

This virus can affect both adults and children. In children, it is also known as fifth disease or erythema infectiousum. Arthritis more commonly happens in adults and women over men.

Clinical Presentation Joint symptoms can occur concurrently with skin rash (erythematous malar rash, "slapped cheek") or soon after eruption. Fever is generally present. In adults, arthritis can occur without fever or rash. The affected joints in adults are typically in the hand, while in children the knee is more commonly affected. The arthritis can be monoarticular, or asymmetric oligoarticular. Overall, joint pain and stiffness is more likely to occur over joint swelling. Symptoms can last for a prolonged period of time from weeks to months. The infection is usually self-limited, however, there is a potential for recurrence or chronic arthritis [54].

Diagnostic Studies Parvovirus B19 can present like a systemic autoimmune rheumatic-like disease with positive laboratory values such as antinuclear antibodies, rheumatoid factor, elevated ESR and CRP. The arthritis is non-erosive and despite the rheumatic-like syndrome, it has not been found to progress to rheumatoid arthritis. To distinguish this from other viruses, a serologic test for parvovirus b19-specific IgM antibody can be performed. Parvovirus DNA can be found in inflamed joints and in other tissues.

Treatment Supportive care for joint manifestations.

Alphaviruses

These viruses are mosquito-borne RNA viruses that appear in countries across the globe. These viruses appear in cycles and re-emerge from time to time as a result of continuous transmission from mosquito to human and other mammals or birds. Transmission is highest during the rainy season. Notable alphaviruses include Ross River virus, Chikungunya virus, Mayaro virus, and Sindbis virus. The incubation period can be for days to weeks. Out of the above, Chikungunya virus is more persistently common with outbreaks in multiple countries. In the USA, it is usually found in travelers [55, 56].

Clinical Presentation In general, infection with an alphavirus will cause fever, arthritis, and rash. The arthritis is typically polyarticular with occasional periarticular and tendinous involvement. Symptoms can last anywhere from weeks to months. The joint symptoms will typically occur prior to a skin rash and may even manifest prior to fever. The rash itself may be short lived (7–10 days) compared to the joint symptoms.

For Chikungunya virus specifically, the arthritis can cause significant, incapacitating pain as the virus invades joint tissues such as synovium and surrounding muscles and replicates causing a release of inflammatory cytokines. Joint symptoms may present in one joint first but will typically have bilateral, symmetric, polyarticular involvement. Symptoms include morning stiffness and edema with decreases in strength due to pain. The virus may be cleared from the joint in a few weeks, but viral RNA has been found to persist in tissues which can lead to chronic arthritis as a result of persistent viral replication, inflammatory or autoimmune response to viral RNA. Older age, prior existing osteoarthritis, and severe acute Chikungunya virus can predispose someone to chronic inflammatory polyarthritis [57].

Treatment Treatment of alphavirus related arthritis should start off with medications such as tylenol and NSAIDs, and other conservative measures such as physical therapy. There are no specific antiviral therapies available. For Chikungunya virus treatment, if conservative medications are ineffective, oral glucocorticoids are the next step. If steroids continue to be ineffective, DMARDs such as methotrexate or sulfasalazine can be considered.

Epstein–Barr Virus (EBV)

Also known as infectious mononucleosis. EBV is transmitted through saliva and stays latent in B-cells. The majority of the population will remain asymptomatic despite infection [49].

Clinical Presentation Of those that become symptomatic, most will have simple arthralgia. However, for those that develop arthritis, there will be large joint swelling along with pain and stiffness. Symptoms are self-limited. Arthrocentesis findings will show inflammatory findings in the synovial fluid.

Treatment Supportive care for joint manifestations.

Varicella

The varicella virus causes chickenpox. Varicella is a rare cause of arthritis, but when present, happens most often in the knee. Despite presentation like a septic bacterial joint, the pain from varicella arthritis is more likely related to nerve pain than pain from the joint itself [49].

Clinical Presentation Symptoms include swelling, pain, stiffness, and decreased range of motion. Varicella typically involves only one joint and will present a few days after the onset of rash. Symptoms are self-limited.

Diagnostic Studies Arthrocentesis should be performed to rule out concomitant bacterial septic arthritis. Synovial fluid analysis will often be non-diagnostic with up to 6000 WBCs per μL and all mononuclear cells.

Treatment Supportive care for joint manifestations.

Human Immunodeficiency Virus (HIV)

HIV infection has a few musculoskeletal syndromes that are related specifically to HIV, but also has syndromes associated with rheumatic diseases. The rheumatic diseases are typically separate from HIV infection but their expressions are affected by

the HIV infection. Some examples include reactive arthritis, septic arthritis, and psoriatic arthritis. The expression of rheumatic diseases may be related to immunodeficiency, immune hyperactivity, dysregulated production or activity of cytokines, or molecular mimicry [49].

HIV-Associated Syndromes

Painful articular syndrome: This presents asymmetrically, normally in lower extremity joints. The pain is typically out of proportion to clinical findings which are usually benign. This syndrome is self-limited and can last for only a day without treatment. This does not progress to an active inflammatory joint process.

HIV-associated arthritis: This typically lower extremity symmetric oligoarticular arthritis is non-erosive and non-destructive. Symptoms can last for weeks and are self-limited without treatment. Arthrocentesis is usually non-diagnostic and diagnostic imaging is normal.

Diffuse infiltrative lymphocytosis syndrome: Causes salivary and lacrimal gland enlargement and can mimic Sjögren's syndrome. This syndrome causes arthralgias but not arthritis [49].

Rheumatic Diseases with HIV Infection

Reactive arthritis: The typical presentation of conjunctivitis, urethritis, and arthritis is less likely to occur. HLA-B27 antigen may be present, but axial involvement is rare. There will likely be enthesopathies and mucocutaneous manifestations. The reactive arthritis will be chronic and relapsing.

Septic arthritis: Staphylococcus aureus is the most common organism, along with others such as *Streptococcus*, *H. influenzae*, and *Salmonella* species. The risk of septic arthritis is higher with CD4 < 200 cells/μL and substance abuse. HIV-associated septic arthritis typically manifests as monoarticular.

Psoriatic arthritis: Severity of the disease can be worse with concomitant HIV infection. Feet and ankle joints are the most severely affected, but there can be knee involvement. It may present with bony deformities and osteolysis, without obvious skin lesions.

Other diseases: Rheumatic and inflammatory diseases will usually not manifest in HIV infection if the CD4 count is low. However, once HIV treatment has begun and immune system function has improved, these syndromes can manifest [49].

Return to Activity Overall, physical and occupational therapy is an important part of a long-term treatment plan for chronic HIV and its comorbid conditions. There is no joint restriction for HIV-associated or related arthritis and maintaining general mobility and functional activity is ideal. Activities and weight bearing are as tolerated and should be progressive [58].

SARS-CoV-2 Infection (COVID-19)

COVID-19 musculoskeletal manifestations include diffuse malaise, arthralgias, and myalgias, which can mimic rheumatic diseases. Manifestation may be oligo- or polyarticular. It has not yet been shown to target specific joints or have specific findings in joint analysis or imaging [40, 59].

Other viruses that can cause knee arthralgias or arthritis not included in this chapter: Rubella, rubella vaccine virus, flaviviruses like dengue and zika, mumps, adenovirus, herpes simplex, and cytomegalovirus.

Return to Activity Since in general, the majority of viral disease is self-limited or treated completely with antivirals, there is no restriction of activity or joint mobilization with viral arthritis. Activity and weight bearing is as tolerated and progressive.

Fungal

Fungal etiologies are rare causes of infectious arthritis and osteomyelitis but need to be kept in the differential diagnosis, particularly in endemic areas. Patients who are immunocompromised either from chronic infection, like HIV, or iatrogenically, are at risk for disseminated fungal infections. One important group are those taking TNF-α inhibitors. Common fungal organisms include blastomycosis, coccidioidomycosis, cryptococcosis, and candida. Other etiologies can include histoplasmosis, and sporotrichosis. Fungal arthritis is usually as a result of hematogenous spread or direct extension of a bony lesion from disseminated disease. Arthrocentesis and synovial fluid analysis can show leukocytes ≤40,000/μL and about 70% neutrophils. Diagnosis of these disorders often requires tissue biopsy with culture or direct visualization of yeast forms on histology. In the context of the knee joint, biopsy of synovium may be needed. Treatment involves aspiration of joint fluid along with lavage. Identification of the pathogen and systemic antifungals are required. In some instances, amphotericin B has been used intraarticularly [60].

Return to Activity Appropriate and complete antifungal therapy generally leads to full recovery without residual joint deficits. Recovery may be prolonged if surgery is required. In general, activity and weight bearing is progressive and as tolerated.

Blastomycosis

Blastomycosis is endemic to the North-Central and Southern United States. It is caused by *Blastomyces dermatitidis*. Musculoskeletal manifestations are most commonly bone pain, swelling and soft tissue abscesses. Infectious arthritis is a less common manifestation, but when it occurs it most commonly affects large joints of the lower extremity including the knee [61].

Radiographs of the knee may show "punched-out" bone lesions.

Coccidioidomycosis

Classically endemic to the southwestern United States (including Arizona, New Mexico and Southern California) and Central America. *Coccidioides immitis* is the most common. The primary site of infection is usually the lungs through inhalation of spores, manifesting as pneumonia. Infection of bones or joints is the result of hematogenous spread and happens weeks to months after exposure. Joint manifestation is typically monoarticular. The knee joint is the most commonly affected joint. Symptoms include pain and stiffness with or without effusion. If infection progresses, imaging may show soft tissue and joint effusion along with bony involvement due to osteomyelitis. Arthrocentesis analysis may have infectious cell count qualities and positive culture. Despite treatment, there is a possibility of recurrence of infection at sites of prior infection.

Valley Fever: This syndrome include infectious pneumonia, arthralgias, and erythema nodosum.

First line treatment for coccidioidomycosis septic arthritis is fluconazole or itraconazole. Amphotericin B may be another option. Depending on severity of joint or bony infection, surgical debridement may be required [62].

Cryptococcosis

Cryptococcosis is generally as a result of inhalation but can also be from direct inoculation from trauma or through the gastrointestinal tract. Classically, it can be found in pigeon droppings. Cryptococcal arthritis is rare and is most frequently a chronic monoarticular arthritis affecting the knee as a result of extension of osteomyelitis. Treatment includes amphotericin B, flucytosine, and fluconazole. In severe or persistent cases, surgery for bony debridement or resection may be necessary [63].

Candida

Musculoskeletal manifestations of candida infections are often due to hematogenous spread to bones or joints. However, exogenous exposure due to trauma, surgery, or intravenous drug use is also possible. Those at risk are typically immunocompromised or suppressed, IV drug users, have chronic indwelling catheters or have used broad spectrum antibiotics. The most recognizable organism is Candida albicans. The knee is a common joint affected by Candida, in both native and prosthetic joints [64].

Clinical Presentation One or more joints may be affected. If a joint is infected, there should be suspicion for surrounding osteomyelitis. Presentation can occur weeks or months after inoculation. Symptoms may be less prominent than bacterial septic arthritis of the knee. There can be pain, tenderness, erythema, effusion, stiffness, along with fever. However, tracts from joint to skin can also occur in severe infections.

Diagnostic Studies Laboratory studies may yield mild leukocytosis and elevated ESR and CRP. X-ray imaging upon initial presentation may be benign but can show erosions and destruction if infection persists. MRI bony signal changes can signify osteomyelitis. Arthrocentesis may show purulent fluid with infectious cell qualities (WBC >20,000 cells/μL, >75% polymorphonuclear leukocytes). Cultures will be positive on standard media.

Treatment Native joint fungal septic arthritis can be treated with oral fluconazole for at least 6 weeks or IV echinocandins for 2 weeks followed by oral fluconazole for 4 weeks. Amphotericin B can also be used. Prosthetic joints will usually need to be surgically removed prior to treating with antifungals as above for 12 weeks. A new prosthesis may be implanted 3–6 months after with antifungals should be given for at least 6 weeks after.

Treatment of osteomyelitis requires a longer course of antifungals for 6–12 months. Susceptibilities of candida species should be performed as fluconazole-resistant species should be treated with echinocandins and voriconazole, or amphotericin B [61, 64].

Mycobacteria

Mycobacterium tuberculosis (TB) can manifest in extrapulmonary structures, more often in the spine (Pott's disease) than in the extremities. Tuberculosis arthritis accounts for about 10% of extrapulmonary TB cases. Those at risk for TB joint infection include immunocompromised state, malnutrition, or advanced kidney disease. Joint manifestation of TB is typically reactivation of disease and can present months to years after initial infection. Current active pulmonary tuberculosis is not usually present. Pathogenesis is related to hematogenous spread. Joint involvement is typically monoarticular in large weight-bearing joints. Of note, HIV co-infection is common. If there is a femur or tibial metaphyseal lesion, it can move through the growth plate and affect the adjacent joint [65, 66].

Clinical Presentation TB arthritis include progressive joint pain and stiffness and will often lack constitutional symptoms classic with other septic arthritis, such as fever and chills. Swelling may or may not be present, and overall is usually absent. Symptoms can progress over a time period of months to years. In osteomyelitis, bone pain is common, and can be associated with soft tissue erythema, edema, sinus tract, or abscess formation.

Poncet disease: This is an acute reactive symmetric polyarthritis affecting both small and large joints. There will be inflammation of the joint but mycobacteria is not found in the joint. Joint symptoms are treated once anti-TB therapy is started and will not have residual joint destruction.

Diagnostic Studies Arthrocentesis and synovial fluid analysis can be done. Synovial fluid will have an average leukocyte count

of 20,000/μL and about 50% neutrophils. Acid-fast stain is positive in only about one-third of cases. Synovial fluid culture is positive about 80% of the time. Synovial tissue biopsy should be performed and is more likely to be positive over fluid culture. Histopathology can show the more classic caseating, or non-caseating granulomas. TB cultures can be delayed due to the slow growth of the organism.

Imaging Imaging studies may show osteolytic lesions in multiple sites, including peripheral erosions at sites of synovial attachment, and joint space narrowing if late in the disease. There can also be soft tissue swelling or calcification, or periarticular osteopenia. MRI can show if the musculoskeletal TB is spreading to adjacent structures.

Treatment Anti-tuberculosis therapy includes rifampin, isoniazid, pyrazinamide, and ethambutol and treatment length is typically longer than for pulmonary TB due to poor penetration of medication. Treatment courses are also longer if the patient is immunosuppressed. Surgical debridement may be required for abscesses or sinus tracts. Surgical stabilization of bony lesions, synovectomy, and joint replacement may be performed depending on severity of disease.

Return to Activities If treated in the early stages, patients typically make a full recovery without residual deficits. Activities and weight bearing are progressive and as tolerated. If joint destruction has occurred, patients will likely require surgery in order to return to baseline level of function.

Atypical Mycobacteria Atypical mycobacteria such as *M. marinum, M. avium-intracellulare, M. terrae, M. kansasii, M. fortuitum, M. chelonae* are found in soil and water and through trauma and direct inoculation can cause chronic arthritis. Diagnosis can be made as above with biopsies and cultures. Treatment depends on susceptibilities to antimicrobials.

References

1. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016;388(10055):2039–52.
2. Brower AC, Flemming DJ. Arthritis in black and white. 2nd ed. Elsevier: Saunders; 1997.
3. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, Gelber AC, Harrold LR, Khanna D, King C, Levy G, Libbey C, Mount D, Pillinger MH, Rosenthal A, Singh JA, Sims JE, Smith BJ, Wenger NS, Bae SS, Danve A, Khanna PP, Kim SC, Lenert A, Poon S, Qasim A, Sehra ST, Sharma TSK, Toprover M, Turgunbaev M, Zeng L, Zhang MA, Turner AS, Neogi T. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). 2020;72(6):744–60.
4. Jablonski K, Young NA, Henry C, Caution K, Kalyanasundaram A, Okafor I, Harb P, Schwarz E, Consiglio P, Cirimotich CM, Bratasz A, Sarkar A, Amer AO, Jarjour WN, Schlesinger N. Physical activity prevents acute inflammation in a gout model by downregulation of TLR2 on circulating neutrophils as well as inhibition of serum CXCL1 and is associated with decreased pain and inflammation in gout patients. PLoS One. 2020;15(10):e0237520.
5. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. N Engl J Med. 2016;374(26):2575–84.
6. Parperis K, Papachristodoulou E, Kakoullis L, Rosenthal AK. Management of calcium pyrophosphate crystal deposition disease: a systematic review. Semin Arthritis Rheum. 2021;51(1):84–94.
7. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: a review. JAMA. 2018;320(13):1360–72. https://doi.org/10.1001/jama.2018.13103.
8. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, Kavanaugh A, McInnes IB, Solomon DH, Strand V, Yamamoto K. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001. https://doi.org/10.1038/nrdp.2018.1. PMID: 29417936.
9. Katz P, Andonian BJ, Huffman KM. Benefits and promotion of physical activity in rheumatoid arthritis. Curr Opin Rheumatol. 2020;32(3):307–14. https://doi.org/10.1097/BOR.0000000000000696.
10. Dall'era M and Wofsy D. Clinical features of systemic lupus erythematosus. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 1413–36.
11. Morgan J, McCarty DJ. Tendon ruptures in patients with systemic lupus erythematosus treated with corticosteroids. Arthritis Rheum. 1974;17(6):1033–6. https://doi.org/10.1002/art.1780170616.
12. Budhram A, Chu R, Rusta-Sallehy S, Ioannidis G, Denburg JA, Adachi JD, Haaland DA. Anti-cyclic citrullinated peptide antibody as a marker of erosive arthritis in patients with systemic lupus erythematosus: a sys-

tematic review and meta-analysis. Lupus. 2014;23(11):1156–63. https://doi.org/10.1177/0961203314540967; Epub 2014 Jul 2.
13. Vaglio A, Grayson PC, Fenaroli P, Gianfreda D, Boccaletti V, Ghiggeri GM, Moroni G. Drug-induced lupus: traditional and new concepts. Autoimmun Rev. 2018;17(9):912–8. https://doi.org/10.1016/j.autrev.2018.03.016; Epub 2018 Jul 10.
14. Fanouriakis A, Bertsias G, Boumpas DT. Treatment of systemic lupus erythematosus. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 1445–7.
15. O'Dwyer T, Durcan L, Wilson F. Exercise and physical activity in systemic lupus erythematosus: a systematic review with meta-analyses. Semin Arthritis Rheum. 2017;47(2):204–15. https://doi.org/10.1016/j.semarthrit.2017.04.003; Epub 2017 Apr 7.
16. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, McGonagle D. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol. 2017;13(12):731–41.
17. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial Spondyloarthritis. N Engl J Med. 2016;374(26):2563–74. https://doi.org/10.1056/NEJMra1406182.
18. Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, Duruoz T, Esbensen BA, Günther KP, Hurkmans E, Juhl CB, Kennedy N, Kiltz U, Knittle K, Nurmohamed M, Pais S, Severijns G, Swinnen TW, Pitsillidou IA, Warburton L, Yankov Z, Vliet Vlieland TPM. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(9):1251–60. https://doi.org/10.1136/annrheumdis-2018-213585; Epub 2018 Jul 11.
19. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The prevalence and incidence of axial and peripheral Spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2017;11(5):631–42. https://doi.org/10.1093/ecco-jcc/jjw199.
20. Zamore R, Bewtra M, Ogdie A. Inflammatory bowel disease-associated arthritis and other enteropathic arthropathies. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 1381–95.
21. Zeidler H, Hudson AP. Reactive arthritis update: spotlight on new and rare infectious agents implicated as pathogens. Curr Rheumatol Rep. 2021;23(7):53. https://doi.org/10.1007/s11926-021-01018-6.
22. Schmitt SK. Reactive arthritis. Infect Dis Clin N Am. 2017;31(2):265–77. https://doi.org/10.1016/j.idc.2017.01.002; Epub 2017 Mar 11
23. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376(10):957–70. https://doi.org/10.1056/NEJMra1505557; Erratum in: N Engl J Med. 2017 May 25;376(21):2097.
24. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3(1):55–78. https://doi.org/10.1016/0049-0172(73)90035-8.

25. Fitzgerald O, Magee C. Psoriatic arthritis. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 1359–77.
26. Millner JR, Barron JS, Beinke KM, Butterworth RH, Chasle BE, Dutton LJ, Lewington MA, Lim EG, Morley TB, O'Reilly JE, Pickering KA, Winzenberg T, Zochling J. Exercise for ankylosing spondylitis: an evidence-based consensus statement. Semin Arthritis Rheum. 2016;45(4):411–27. https://doi.org/10.1016/j.semarthrit.2015.08.003; Epub 2015 Aug 18.
27. Yee AM. Sarcoidosis: rheumatology perspective. Best Pract Res Clin Rheumatol. 2016;30(2):334–56. https://doi.org/10.1016/j.berh.2016.07.001; Epub 2016 Aug 28.
28. Bechman K, Christidis D, Walsh S, Birring SS, Galloway J. A review of the musculoskeletal manifestations of sarcoidosis. Rheumatology (Oxford). 2018;57(5):777–83. https://doi.org/10.1093/rheumatology/kex317.
29. Korsten P, Sweiss NJ, Baughman RP. Sarcoidosis. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 2088–104.
30. Sweiss NJ, Patterson K, Sawaqed R, Jabbar U, Korsten P, Hogarth K, Wollman R, Garcia JG, Niewold TB, Baughman RP. Rheumatologic manifestations of sarcoidosis. Semin Respir Crit Care Med. 2010;31(4):463–73. https://doi.org/10.1055/s-0030-1262214; Epub 2010 Jul 27.
31. Vivino FB. Sjogren's syndrome: clinical aspects. Clin Immunol. 2017;182:48–54. https://doi.org/10.1016/j.clim.2017.04.005; Epub 2017 Apr 17.
32. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018;93:24–36. https://doi.org/10.1016/j.jaut.2018.07.018; Epub 2018 Aug 1.
33. Hsu JJ, Lee TC, Sandborg CI. Clinical features and treatment of juvenile idiopathic arthritis. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 1915–9.
34. Kermani TA, Warrington KJ. Polymyalgia rheumatica. Lancet. 2013;381(9860):63–72. https://doi.org/10.1016/S0140-6736(12)60680-1; Epub 2012 Oct 8. Erratum in: Lancet. 2013 Jan 5;381(9860):28.
35. Kerr DA, Rosenberg AE. Tumors and tumor-like lesions of joints and related structures. In: Firestein Gary S, Budd Ralph C, Gabriel Sherine E, McInnes Iain B, O'Dell James R, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 2174–80.
36. Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented

villonodular synovitis). Orthop Traumatol Surg Res. 2017;103(1S):S91–7. https://doi.org/10.1016/j.otsr.2016.11.002; Epub 2017 Jan 2.
37. Davis RI, Hamilton A, Biggart JD. Primary synovial chondromatosis: a clinicopathologic review and assessment of malignant potential. Hum Pathol. 1998;29(7):683–8.
38. Neumann JA, Garrigues GE, Brigman BE, Eward WC. Synovial Chondromatosis. JBJS Rev. 2016;4(5):e2. https://doi.org/10.2106/JBJS.RVW.O.00054.
39. Covey CJ, Shmerling RH. Approach to the adult with unspecified knee pain. In Fields KB, Grayzel J, editors. UptoDate. 2020. https://www.uptodate.com/contents/approach-to-the-adult-with-unspecified-knee-pain?search=viral%20knee%20pain&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1748999242.
40. Helfgott SM. Monoarthritis in adults: etiology and evaluation. In: Shmerling RH, Curtis MR, editors. UptoDate. 2021. https://www.uptodate.com/contents/monoarthritis-in-adults-etiology-and-evaluation?search=fungal%20arthritis&source=search_result&selectedTitle=3~33&usage_type=default&display_rank=3#H65842858.
41. Goldenberg DL, Sexton DJ. Septic arthritis in adults. In: Spelman D, Hall KK, editors. UptoDate. 2022. https://www.uptodate.com/contents/septic-arthritis-in-adults?search=fungal%20joint&source=search_result&selectedTitle=2~36&usage_type=default&display_rank=2#H4533994.
42. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine. 20th ed. New York: McGraw Hill; 2018.
43. Sholter DE, Russell AS. Synovial fluid analysis. In: Shmerling RH, Calderwood SB, Curtis MR, editors. UptoDate. 2021. https://www.uptodate.com/contents/synovial-fluid-analysis?search=viral%20knee%20pain&topicRef=253&source=see_link.
44. Klausner JD. Disseminated gonococcal infection. In: Marrazzo J, Bloom A, editors. UptoDate. 2021. https://www.uptodate.com/contents/disseminated-gonococcal-infection?search=viral%20knee%20pain&topicRef=253&source=see_link.
45. Ayoade F, Li DD, Mabrouk A, et al. Prosthetic joint infection. [Updated 2021 Sep 28]. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK448131/.
46. Berbari E, Baddour LM, Chen AF. Prosthetic joint infection: epidemiology, microbiology, clinical manifestations, and diagnosis. In: Spelman D, Hall KK, editors. UptoDate. 2021. https://www.uptodate.com/contents/prosthetic-joint-infection-epidemiology-microbiology-clinical-manifestations-and-diagnosis?search=fungal%20joint&topicRef=2466&source=related_link.

47. Berbari E, Baddour LM, Chen AF. Prosthetic joint infection: treatment. In: Spelman D, Hall KK, editors. UptoDate. 2021. https://www.uptodate.com/contents/prosthetic-joint-infection-treatment?search=fungal%20arthritis&source=search_result&selectedTitle=7~33&usage_type=default&display_rank=7.
48. Mur I, Jordán M, Rivera A, Pomar V, González JC, López-Contreras J, Crusi X, Navarro F, Gurguí M, Benito N. Do prosthetic joint infections worsen the functional ambulatory outcome of patients with joint replacements? A retrospective matched cohort study. Antibiotics (Basel). 2020;9(12):872. https://doi.org/10.3390/antibiotics9120872.
49. Moore TL, Syed R. Viruses that cause arthritis. In: Schur PH, Romain PL, editors. UptoDate. 2021. https://www.uptodate.com/contents/viruses-that-cause-arthritis?search=viral%20knee%20pain&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H17.
50. Chopra S, Lai M. Hepatitis A virus infection: treatment and prevention. In: Leder K, Rand EB, Baron EL, editors. UptoDate. 2021. https://www.uptodate.com/contents/hepatitis-a-virus-infection-treatment-and-prevention?search=hepatitis%20A%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1235658502.
51. Lok ASF. Hepatitis B virus: overview of management. In: Esteban R, Mitty J, editors. UptoDate. 2021. https://www.uptodate.com/contents/hepatitis-b-virus-overview-of-management?search=hepatitis%20B%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1521734005.
52. Feld JJ. Clinical manifestations, diagnosis and treatment of acute hepatitis C virus infection in adults. In: Di Bisceglie AM, Bloom A, editors. UptoDate. 2020. https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-acute-hepatitis-c-virus-infection-in-adults?search=acute%20hepatitis%20c%20treatment&source=search_result&selectedTitle=1~86&usage_type=default&display_rank=1.
53. Chopra S, Pockros PJ. Overview of the management of chronic hepatitis c virus infection. In: Di Bisceglie AM, Bloom A, editors. UptoDate. 2020. https://www.uptodate.com/contents/overview-of-the-management-of-chronic-hepatitis-c-virus-infection?search=hepatitis%20c%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1818295792.
54. Jordan JA. Clinical manifestations and diagnosis of parvovirus B19 infection. In: Hirsch MS, Edwards MS, editors. UptoDate. 2021. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-parvovirus-b19-infection?search=viral%20knee%20pain&topicRef=5584&source=see_link.
55. Richards MJ. Ross river virus infection. In: Hirsch MS, Hall KK, editors. UptoDate. 2021. https://www.uptodate.com/contents/ross-river-virus-

infection?search=viral%20knee%20pain&topicRef=5584&source=see_link#H20298699.
56. Milner JJ, Lenschow DJ, Wilson ME. Chikungunya fever: treatment and prevention. In: Schur PH, Hirsch MS, Romain PL, Baron EL, editors. UptoDate. 2021. https://www.uptodate.com/contents/chikungunya-fever-treatment-and-prevention?sectionName=Chronic%20arthritis&search=viral%20knee%20pain&topicRef=3024&anchor=H4008376777&source=see_link#H4008376777.
57. Wilson ME, Lenschow DJ, Milner JJ. Chikungunya fever: epidemiology, clinical manifestations, and diagnosis. In: Hirsch MS, Schur PH, Baron EL, Romain PL, editors. UptoDate. 2021. https://www.uptodate.com/contents/chikungunya-fever-epidemiology-clinical-manifestations-and-diagnosis?search=viral%20knee%20pain&topicRef=5584&source=see_link#H810986770.
58. deBoer H, Andrews M, Cudd S, Leung E, Petrie A, Chan Carusone S, O'Brien KK. Where and how does physical therapy fit? Integrating physical therapy into interprofessional HIV care. Disabil Rehabil. 2019;41(15):1768–77. https://doi.org/10.1080/09638288.2018.1448469; Epub 2018 Mar 13.
59. Mikuls TR, Johnson SR, Gravallese EM, Saag KG. COVID-19: care of adult patients with systemic rheumatic disease. In: St Clair EW, Goldenberg DL, Romain PL, Curtis MR, editors. UptoDate. 2021. https://www.uptodate.com/contents/covid-19-care-of-adult-patients-with-systemic-rheumatic-disease?sectionName=COVID-19%20as%20a%20risk%20factor%20for%20rheumatologic%20disease&search=fungal%20arthritis&topicRef=1820&anchor=H1119802728&source=see_link#H1119802728.
60. Bariteau JT, Waryasz GR, McDonnell M, Fischer SA, Hayda RA, Born CT. Fungal osteomyelitis and septic arthritis. J Am Acad Orthop Surg. 2014;22(6):390–401. https://doi.org/10.5435/JAAOS-22-06-390.
61. Ruderman EM, Flaherty JP. Fungal infections of bones and joints. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors. Kelley and Firestein's textbook of rheumatology. 11th ed. Philadelphia: Elsevier; 2021. p. 2022–32.
62. Blair JE, Ampel NM. Manifestations and treatment of nonmeningeal extrathoracic coccidioidomycosis. In: Kauffman CA, Bogorodskaya M, editors. UptoDate. 2021. https://www.uptodate.com/contents/manifestations-and-treatment-of-nonmeningeal-extrathoracic-coccidioidomycosis?search=c%20immitis%20arthritis&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3.
63. Mokrzycki A, Meyssonnier V, Heym B, Aubert T, Mouton A, Marmor S, Zeller V. Cryptococcal arthritis in an immunocompetent migrant. J Travel Med. 2020;27(4):taaa028. https://doi.org/10.1093/jtm/taaa028.
64. Kauffman CA. Candida osteoarticular infections. In: Sexton DJ, Hall KK, editors. UptoDate. 2021. https://www.uptodate.com/contents/candida-osteoarticular-infections?search=fungal%20joint&source=search_result&selectedTitle=1~36&usage_type=default&display_rank=1.

65. Stout S. Bone and joint tuberculosis. In: Bernardo J, Baron EL, editors. UptoDate. 2021. https://www.uptodate.com/contents/bone-and-joint-tuberculosis?search=fungal%20arthritis&topicRef=1820&source=see_link.
66. Al-Sayyad MJ, Abumunaser LA. Tuberculous arthritis revisited as a forgotten cause of monoarticular arthritis. Ann Saudi Med. 2011;31(4):398–401. https://doi.org/10.4103/0256-4947.83210.