*M. tuberculosis* (and occasionally non-tuberculous mycobacteria) and *Brucella* species. Two sets of aerobic and anaerobic blood cultures and ESR and CRP should be obtained; in addition, *Brucella* blood cultures and serologic tests should be obtained in those in areas endemic for brucellosis, fungal blood cultures in those with relevant epidemiologic or host risk factors, and a purified protein derivative test and interferon-γ release assay considered in those at risk for tuberculosis. Patients suspected of having native vertebral osteomyelitis based on clinical, laboratory, and imaging studies, with *S. aureus*, *Staphylococcus lugdunensis*, or *Brucella* bloodstream infection or, in an endemic setting, a positive *Brucella* serology, do not need further testing. For all others, imaging-guided aspiration/biopsy of a disc space or vertebral endplate is recommended, with specimens submitted for Gram stain and aerobic and anaerobic culture and, if adequate tissue can be obtained, histopathology. If results are negative or inconclusive (eg, *Corynebacterium* species is isolated), a second imaging-guided aspiration biopsy, percutaneous endoscopic discectomy and drainage procedure, or open excisional biopsy, should be considered to collect additional specimens for repeat and additional testing. Readers are referred to a guideline that provides greater detail on the diagnosis of native vertebral osteomyelitis in adults [401]. Further studies are needed to define ideal diagnostic approaches for vertebral osteomyelitis.

Molecular diagnostics may be performed on bone biopsies but are not considered first-line diagnostic tests. Microorganism-specific NAATs or a broader approach, such as 16S ribosomal RNA gene PCR/sequencing (for bacterial detection) [402], may be considered. One strategy is to temporarily set aside a specimen with this type of testing performed if cultures are negative and other findings point to a diagnosis of infection; another is to perform molecular testing on formalin-fixed paraffin-embedded tissue collected for histopathologic evaluation. *K. kingae* may require molecular detection methods for diagnosis, with *K. kingae* PCR or 16S ribosomal RNA gene PCR/sequencing [402].

#### Infections of Native Joints

Joints can be hematogenously seeded by bacteria, or seeded by direct inoculation, or from a contiguous focus, with a majority of infections being monoarticular. *S. aureus*, *Streptococcus* species, and *Neisseria gonorrhoeae* are common causes of septic arthritis of native joints, followed by gram-negative bacilli, which mainly cause septic arthritis in neonates, older individuals, persons who inject drugs, and the immunocompromised, and other gram-positive bacteria. *K. kingae* is the most common etiology of bacterial joint infection in children younger than 4 years. Viruses, including parvovirus B19, chikungunya virus, and rubella, among others, may be associated with arthritis (Table 46). Subacute or chronic infectious arthritis may be caused by *M. tuberculosis* and non-tuberculosis mycobacteria, *Borrelia burgdorferi, Candida* species, *Blastomyces dermatitidis, Coccidioides immitis/posadasii, Histoplasma capsulatum, Sporothrix schenckii, Cryptococcus neoformans/gattii,* and *Aspergillus* species, among others. Septic bursitis, which usually involves the prepatellar, olecranon, or trochanteric bursae, is usually caused by *S. aureus*.

Although peripheral blood white cell count, ESR, and CRP are often elevated, they are non-specific. Arthrocentesis of a septic joint usually reveals purulent, low-viscosity synovial fluid with an elevated neutrophil count. Traditionally, a synovial fluid leukocyte count more than 50 000 cells/mm$^3$ was considered to suggest septic arthritis; however, lower counts do not exclude the diagnosis. Ideally, synovial fluid from native joints should be submitted for Gram stain, and cultured in aerobic and anaerobic blood culture bottles. If synovial fluid Gram stain and culture are negative, molecular testing of synovial fluid with a multiplex PCR panel or 16S ribosomal RNA gene PCR/sequencing [402], should be considered; biopsy of the synovium for Gram stain, aerobic and anaerobic cultures, and histopathologic evaluation, with or without fungal and mycobacterial stains and cultures may be considered. Concomitant or secondary bacteremia or fungemia occurs sporadically in patients with septic arthritis; thus, blood cultures collected during febrile episodes are recommended. Some less common agents, such as *K. kingae*, may require molecular detection methods for optimal diagnosis; *K. kingae* PCR is available as part of a recently FDA-cleared multiplex PCR panel for testing synovial fluid and offered by individual laboratories as single- or multiple- target laboratory developed tests. *N. gonorrhoeae* is also included as part of the recently FDA-cleared multiplex PCR panel for testing synovial fluid.

#### Periprosthetic Joint Infection

A special category of infection exists for periprosthetic joint infection, which may involve knee, hip, shoulder, elbow, or other prostheses [403]. Staphylococci, including not just *S. aureus* but also the coagulase-negative staphylococci, especially *Staphylococcus epidermidis*, are particularly common causes, but many other organisms, including streptococci, enterococci, aerobic Gram-negative bacilli, anaerobic bacteria (eg, *Cutibacterium acnes, Finegoldia magna*) and fungi, can be involved (Table 47). *C. acnes* is particularly common in shoulder arthroplasty infection.

The diagnosis of periprosthetic joint infection and definition of its microbiology is ideally made pre-operatively, but if this is not possible, diagnosis and, if present, definition of microbiology should be pursued at the time of revision or resection arthroplasty. Readers are referred to recently published guidance on the diagnosis of periprosthetic joint infection [405–407]. Preoperatively, ESR and CRP are recommended (some also use D-dimer), as is arthrocentesis for synovial fluid cell count and differential and culture, ideally in aerobic and anaerobic