magnesium. Amino acid malabsorption occurs; protein metabolism is complicated further by loss of albumin in the lumen of the damaged small bowel.[55]

Most of the functional changes in tropical sprue may be related to small bowel mucosal damage consistent with the morphologic changes seen, but the hormonal regulation of the gut is also dysfunctional in this disease.[56] Postprandial insulin and gastric inhibitory peptide are reduced in tropical sprue; enteroglucagon and motilin levels are increased. In chronic tropical sprue, gastric acid secretion and secretion of intrinsic factor may also be affected. Transit time through the small bowel is slowed, as measured by breath hydrogen testing. [57–59]

In the few studies of colonic function in tropical sprue that have been done, the ability of the colon to absorb water is decreased in patients compared with controls.[60] There is speculation that the dysfunction of colonic cells may be related to damage by excess fatty acids in the gut lumen or bacterial toxins or infection. Although there is physiologic confirmation of the ability of fatty acids to disturb the absorptive function of colonocytes and small bowel enterocytes, data suggesting that colonic infections are important in the pathogenesis of tropical sprue are lacking.

HISTOPATHOLOGY

Tropical Sprue

Partial villous atrophy is the hallmark histologic change seen in the small bowel in tropical sprue, as opposed to the flattened mucosa that is characteristic of celiac sprue.[61] The villi in tropical sprue progressively shorten and thicken, forming fused leaves after about 4 months of illness.[62] These histologic changes are seen in the jejunum and the ileum, where the changes in absorption also are localized. These histologic changes are not specific for tropical sprue but may be present in severe folate deficiency or with bacterial overgrowth. In distinction, in celiac disease, blunting of villi and crypt hyperplasia are seen and lymphocytes are noted to infiltrate the crypts.

Microscopically, the mucosa is thin, with an infiltrate of chronic inflammatory cells consisting of plasma cells, histiocytes, lymphocytes, and eosinophils. As noted, these lymphocytes have been characterized, and IgA-, IgG-, and IgM-producing B lymphocytes are present in numbers equal to those of asymptomatic control patients,[40,41] suggesting that this is not a part of the pathogenesis of the illness. An increased mitotic index can be seen in the crypt cells; the nuclei of the crypt cells may also appear megaloblastic.[55,63] An increased number of goblet cells may be present, and lipoid vacuoles have been seen within the basement membrane. To date, there is no convincing evidence that tropical sprue is an immunologically mediated disease.

Environmental Enteric Dysfunction

EED is currently thought to be a consequence of continuous exposure to enteric pathogens via the oral-fecal route leading to intestinal mucosal inflammation, altered barrier integrity, and reduced absorption.[9] In addition, since the gut microbiome modulates immune and inflammatory responses, maintains intestinal barrier integrity, and determines nutritional status,[64] it is possible that dysbiosis or alterations in the composition of the microbiome may lead to dysregulated inflammatory responses, impaired barrier function, increased microbial translocation across the gut, and mucosal or systemic inflammation.[4,6] Mucosal immune responses, including T-cell activation as well as B-cell and innate immune derangements, are implicated in EED.[6] However, the underlying mechanisms are not completely understood. EED has also been reported to be associated with metabolic derangements, including carnitine deficiency, altered fatty acid oxidation, and altered bile acid metabolism.[65,66]

DIAGNOSIS

Tropical Sprue

Because the symptom complex of tropical sprue is nonspecific, the travel and exposure history of the patient are crucial in making the diagnosis. Tropical sprue should be considered in a patient who presents with chronic diarrhea, weight loss, and evidence of malabsorption. Attempts should be made to ascertain the onset of the diarrheal illness, duration of diarrheal illness, degree of weight loss, frequency and character of the stool, and any other systemic complaints, such as prolonged fever, jaundice, or itching, that might suggest alternative explanations for the diarrheal illness. Information regarding travel to, residence in, or emigration from the tropics should be requested. Although there have been sporadic case reports of mild spruelike illnesses occurring after diarrheal illnesses in temperate climates, this so-called temperate sprue is rare and a history of exposure to an endemic area should be present to even consider the diagnosis of tropical sprue.[43]

Pertinent medical history should also be obtained. There are no diagnostic physical findings for tropical sprue. Cheilosis, stomatitis, glossitis, rashes, dermatitis, koilonychia, muscle pain or weakness, peripheral neuropathy, or edema can suggest deficiencies of iron, zinc, vitamin B_{12}, folate, vitamins D and E, or protein, but these are usually secondary manifestations. Deficiencies of any of these nutrients could be present in tropical sprue because of malabsorption by the damaged small bowel.

Laboratory evaluation of a patient with suspected tropical sprue can be minimal or extensive, depending on the degree of suspicion and the urgency for diagnosis. A simple, complete blood count showing a macrocytic anemia in a high-risk patient in the appropriate clinical setting could be sufficient to proceed with other, more confirmatory diagnostic tests, such as small bowel biopsies. A more complete laboratory evaluation includes serum vitamin B_{12} and red blood cell folate levels, serum carotene concentration, or, preferably, a 72-hour fecal fat determination. Stool examination to exclude *Giardia* is useful; stool culture looking for the usual acute bacterial pathogens is less likely to be helpful in chronic diarrhea. Testing for human immunodeficiency virus may be appropriate to help define the likelihood of opportunistic intestinal infections.

Ultimately, a small bowel series with small bowel follow-through showing flattened mucosal folds, luminal dilatation, or flocculation of the barium meal can suggest tropical sprue.[67] An upper endoscopy with duodenal aspirate for parasites and biopsy can be diagnostic of tropical sprue in the appropriate clinical setting. Enhanced magnification endoscopy has been shown to be more sensitive in detecting villous atrophy than standard endoscopy and may assist in making a noninvasive diagnosis of sprue. In a study of 15 patients diagnosed with sprue by intestinal biopsy in Caracas, Venezuela, atrophy was demonstrated in 93% of patients by enhanced magnification endoscopy, whereas standard endoscopy was able to detect atrophy in only 20% of patients.[68] Documentation of abnormal transit time by small bowel follow-through or breath hydrogen testing, which also can imply bacterial overgrowth, is suggestive of but is not diagnostic of tropical sprue. The differential diagnosis that must be considered in a patient with chronic diarrhea, weight loss, and malabsorption, even in a clinical setting consistent with tropical sprue, should include giardiasis, cryptosporidiosis, coccidiosis (*Cystoisospora belli*), capillariasis, strongyloidiasis, celiac sprue (gluten enteropathy), lymphoma, intestinal tuberculosis, blind loop syndrome, pancreatic tumors, Whipple disease, and microsporidia-associated human immunodeficiency virus enteropathy. If diagnosis remains obscure, biopsy is considered to be very sensitive and will allow the syndromes to be clearly differentiated. Celiac disease, or gluten enteropathy, can be more definitively diagnosed by serologic testing for antigliadin or antiendomysial antibodies.

Environmental Enteric Dysfunction

A definitive diagnosis of histopathologic changes associated with EED requires small intestine biopsy. However, concerns about safety, cost, and ethical considerations preclude the routine use of biopsy for diagnosis. Functional changes associated with EED, including impaired gut barrier integrity or increased intestinal permeability, malabsorption, mucosal injury and regeneration, and chronic inflammation, have been proposed as biomarkers of EED.[4,6,9] However, although several studies in search of biomarkers characteristic of EED have been performed, to date there is no single biomarker that can be used to diagnose this syndrome.[7] Potential biomarkers associated with functional changes in EED are described below.

Increased Intestinal Permeability/Impaired Gut Barrier Integrity

Dual sugar absorption tests such as the lactulose:mannitol (L:M) ratio are the most widely used biomarker to assess increased intestinal

permeability or impaired gut barrier integrity.[4,6,9] These tests employ sugars that are not metabolized and are excreted intact in the urine. Large sugars such as the disaccharide lactulose do not normally cross the gut mucosal barrier unless intestinal permeability is increased, and small sugars such as the monosaccharide mannitol are absorbed in proportion to small intestine absorptive capacity. Both sugars are administered orally, and their levels are measured in the blood or urine and expressed as a ratio. In subjects with increased intestinal permeability or impaired barrier integrity, the L:M ratio is higher. Increased L:M ratios have been reported in asymptomatic children as well as those with diarrhea in Africa, Asia, and South America. Studies in the Gambia have reported an inverse relationship between L:M ratio and height-for-age.[69] However, other studies have not found similar associations.[4] Possible reasons for this variation include differences in the assay protocol, analytic and reporting methods, and criteria such as breastfeeding, fasting status, dose of sugar administered, and type and timing of sample collected.[4,9] More recent studies have not shown a correlation between L:M ratios and other biomarkers.

Fecal α_1-antitrypsin, a serum glycoprotein and protease inhibitor, is another biomarker of increased intestinal permeability and protein loss.[9] It is not normally present in the diet and is not actively secreted or absorbed. Claudins and zonulin are tight junction proteins that form barriers between intestinal epithelial cells.[7] However, none of these markers is specific for EED.

Intestinal Damage and Repair

A biomarker of small intestine mucosal damage is citrulline, a nonprotein amino acid that is minimally present in the diet, plasma levels of which reflect enterocyte mass and function.[4,9] Plasma citrulline levels depend on de novo synthesis by proximal gut epithelial cells and are reduced in EED. Intestinal fatty acid binding protein is a small intestine epithelial protein that is released into the circulation after injury to the epithelium.[7] The regenerating islet-derived proteins REG1α and REG1β have been proposed as markers of intestinal injury and repair, and therefore potentially of EED.[9] Glucagon-like peptide 2 is a trophic factor released by enteroendocrine L cells of the ileum that aids in mucosal regeneration.[7] However, none of these potential biomarkers is specific for EED. A recent study suggested that optical biopsy may be a potential minimally invasive technique for diagnosing EED.[70]

Mucosal and Systemic Inflammation

A number of markers of mucosal and systemic inflammation have been proposed as biomarkers of EED.[4,6,7,9] Mucosal inflammatory markers include fecal calprotectin, a stable calcium- and zinc-binding protein produced by neutrophils and monocytes; lactoferrin, an iron-binding glycoprotein produced by neutrophils; myeloperoxidase, a marker of neutrophil activity; and neopterin, which is produced by macrophages and dendritic cells in response to interferon-γ, produced by activated T cells. Calprotectin and lactoferrin levels are not reliable in breastfed children since these proteins are secreted in breast milk.[71] Systemic inflammatory markers include proinflammatory cytokines (interleukin [IL]-1β, IL-15, IL-17, tumor necrosis factor-α, interferon-γ, and granulocyte-macrophage colony-stimulating factor) and antiinflammatory cytokines (IL-4, IL-6, and IL-10)[9] as well as C-reactive protein and α1-acid glycoprotein, both acute-phase reactants.

Once again, none of these markers is specific for EED.

Microbial Translocation and Immune Activation

Translocation of microbes or their products across the gut leading to immune activation is believed to contribute significantly to the pathogenesis of EED.[9] Biomarkers for these processes may also serve as biomarkers of EED. These include stool neopterin, plasma lipopolysaccharide (LPS)-specific and flagellin-specific antibodies, LPS core antibody (EndoCAb), LPS binding protein, and circulating soluble CD14.[4,9] However, many of these are biomarkers of other inflammatory diseases as well, so they are not specific for EED, and assays for some of them have not been standardized.

Fecal Messenger mRNA Transcripts

Recent studies in Africa have suggested that levels of specific fecal messenger RNA transcripts for proteins involved in immune activation and inflammation may serve as biomarkers of EED using the L:M ratio as a standard.[72–74] These transcripts include those for CD53, CDX1, HLA-DRA, tumor necrosis factor-α, S100A8, MUC12, and REG1α.

THERAPY

Tropical Sprue

Treatment with folate alone improves the symptoms of tropical sprue, especially those related to anemia, but does not cure the diarrhea. Combination therapy with tetracycline and folate seems to be most effective in symptom resolution and cure of diarrhea with promotion of weight gain.[75,76] Treatment with 250 mg of tetracycline four times daily and 5 mg of folate daily for 1 month has been effective for travelers with tropical sprue, but therapy must be prolonged for 6 months or longer for residents of the tropics who have had disease of long duration. Even with prolonged therapy, relapses have been seen in this population, although these may have been caused by reexposure to an infecting organism and represent recurrent rather than relapsing disease.[77] Reports have suggested that tropical sprue in the Caribbean is more amenable to therapy than sprue in India, but these studies are difficult to compare.[78] Poorly absorbed sulfa drugs are an acceptable alternative to tetracycline in children or pregnant women.[79] A favorable symptomatic response to therapy with folate and antibiotics can provide additional evidence that tropical sprue was the cause of chronic diarrhea and malabsorption in a patient; however, even this is not specific because bacterial overgrowth in a blind loop syndrome patient would also be expected to respond. Lack of response to treatment should lead to additional diagnostic evaluation to include antibodies to gliadin or endomysium or small bowel biopsy.

Environmental Enteric Dysfunction

Several interventions to treat EED have been attempted and others are currently in development or testing. Nutritional interventions such as vitamin A, zinc, glutamine, glycine, and multiple micronutrients have yielded variable results depending on the study.[9] Treatment with the probiotic *Lactobacillus rhamnosus* GG and the antibiotic rifaximin showed no significant differences in clinical or growth outcomes.[9] L-Alanyl-L-glutamine improved weight-for-age and weight-for-height but not height-for-age.[8] Albendazole administration did not result in significant improvement in anthropometry.[8] Trials of ω-3 long-chain polyunsaturated fatty acid, a dietary essential fatty acid, resulted in improvement in mid-upper arm circumference at 9 and 12 months.[8] In a clinical trial of the effect of azithromycin on immunogenicity of oral poliovirus vaccine, biomarkers of EED were reduced although there was no effect on the immunogenicity of the vaccine, suggesting that this antibiotic may be useful in EED.[80] Several trials of WaSH interventions on nutritional status in children have been performed. Overall, these interventions had a very modest impact on stunting but not on wasting or underweight.[81] Several other trials of WaSH interventions are ongoing.[81]

Key References

The complete reference list is available online at Expert Consult.

1. Ramakrishna BS. Tropical sprue: a riddle wrapped in a mystery inside an enigma. *Indian J Med Res*. 2013;137:12–14.
35. Andersson AF, Lindberg M, Jakobsson H, et al. Comparative analysis of human gut microbiota by barcoded pyrosequencing. *PLoS ONE*. 2008;3:e2836.
45. Ghoshal UC, Kumar S, Misra A, et al. Pathogenesis of tropical sprue: a pilot study of antroduodenal manometry, duodenocaecal transit time and fate induced ileal break. *Indian J Med Res*. 2013;137:63–72.
68. Lo A, Guelrud M, Essenfeld H, et al. Classification of villous atrophy with enhanced magnification endoscopy in patients with celiac disease and tropical sprue. *Gastrointest Endosc*. 2007;66:382–386.

References

1. Ramakrishna BS. Tropical sprue: a riddle wrapped in a mystery inside an enigma. *Indian J Med Res*. 2013;137:12–14.
2. Bartholomew C. William Hillary and sprue in the Caribbean: 230 years later. *Gut Festschr*. 1989;30:17–21.
3. Korpe PS, Petri WA Jr. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med*. 2012;18:328–336.
4. Keusch GT, Denno DM, Black RE, et al. Environmental enteric dysfunction: pathogenesis, diagnosis, and clinical consequences. *Clin Infect Dis*. 2014;59(suppl 4):S207–S212.
5. Keusch GT, Rosenberg IH, Denno DM, et al. Implications of acquired environmental enteric dysfunction for growth and stunting in infants and children living in low- and middle-income countries. *Food Nutr Bull*. 2013;34:357–364.
6. Marie C, Ali A, Chandwe K, et al. Pathophysiology of environmental enteric dysfunction and its impact on oral vaccine efficacy. *Mucosal Immunol*. 2018;11:1290–1298.
7. Harper KM, Mutasa M, Prendergast AJ, et al. Environmental enteric dysfunction pathways and child stunting: a systematic review. *PLoS Negl Trop Dis*. 2018;12:e0006205.
8. Crane RJ, Jones KD, Berkley JA. Environmental enteric dysfunction: an overview. *Food Nutr Bull*. 2015;36(1 suppl):S76–S87.
9. Syed S, Ali A, Duggan C. Environmental enteric dysfunction in children. *J Pediatr Gastroenterol Nutr*. 2016;63:6–14.
10. Owino V, Ahmed T, Freemark M, et al. Environmental enteric dysfunction and growth failure/stunting in global child health. *Pediatrics*. 2016;138.
11. Klipstein FA, Samloff IM, Smarth G, et al. Treatment of overt and subclinical malabsorption in Haiti. *Gut*. 1969;10:315–322.
12. Klipstein FA, Corcino JJ. Seasonal occurrence of overt and subclinical tropical malabsorption in Puerto Rico. *Am J Trop Med Hyg*. 1974;23:1189–1196.
13. Gorbach SL, Banwell JG, Jacobs B, et al. Tropical sprue and malnutrition in West Bengal. *Am J Clin Nutr*. 1970;23:1515–1558.
14. Mathan VI, Baker SJ. Epidemic tropical sprue and other epidemics of diarrhea in South Indian villages. *Am J Clin Nutr*. 1968;21:1077–1087.
15. Jones TC, Dean AG, Parker GW. Seasonal gastroenteritis and malabsorption at an American military base in the Philippines. *Am J Epidemiol*. 1973;95:128–139.
16. Hanif FM, Luck NH, Abbas Z, et al. Prevalence and characteristics of duodenal villous atrophy in renal transplant patients presenting with persistent diarrhea in a developing country. *Exp Clin Transplant*. 2016;14:146–152.
17. Thomas G, Clain DJ, Wicks CB. Tropical enteropathy in Rhodesia. *Gut*. 1976;17:888–894.
18. Haeney MR, Montgomery RD, Schneider R. Sprue in the Middle East: five case reports. *Gut*. 1974;15:377–386.
19. Mathan VI, Ignatius M, Baker SJ. A household epidemic of tropical sprue. *Gut*. 1966;7:490–496.
20. Schorling JB, Wanke CA, Schorling SK, et al. A prospective study of persistent diarrhea in children in an urban Brazilian slum. *Am J Epidemiol*. 1990;132:144–156.
21. Lindenbaum J, Kent TH, Sprine H. Malabsorption and jejunitis in American Peace Corps volunteers in Pakistan. *Ann Intern Med*. 1966;65:1201–1209.
22. Montgomery RD, Beale DJ, Sammons HG, et al. Postinfective malabsorption: a sprue syndrome. *BMJ*. 1973;2:265–268.
23. Lauer JM, Duggan CP, Ausman LM, et al. Unsafe drinking water is associated with environmental enteric dysfunction and poor growth outcomes in young children in rural southwestern Uganda. *Am J Trop Med Hyg*. 2018;99:1606–1612.
24. Davis JS, Klipstein FA. Tropical sprue in visitor to Mexico. *Lancet*. 1985;1:454.
25. Klipstein FA, Falaiye JM. Tropical sprue in expatriates from the tropics living in the continental United States. *Medicine (Baltimore)*. 1969;48:475–491.
26. Chacko A, Begum A, Mathan VI. Absorption of nutrient energy in southern Indian control subjects and patients with tropical sprue. *Am J Clin Nutr*. 1984;40:771–775.
27. Haddock L, Vazquez MDC, Rivera R, et al. The kinetics of D3–3H metabolism in tropical sprue. *P R Health Sci J*. 1985;4:47–56.
28. Appelbaum PC, Moshal MG, Hift W, et al. Intestinal bacteria in patients with tropical sprue. *S Afr Med J*. 1980;57:1081.
29. Bhat P, Shantakumari S, Rajan D, et al. Bacterial flora of the gastrointestinal tract in southern Indian control subjects and patients with tropical sprue. *Gastroenterology*. 1972;62:11–21.
30. Tomkins AM, Drasbar BS, James WPT. Bacterial colonisation of jejunal mucosa in acute tropical sprue. *Lancet*. 1975;1:59–62.
31. Nataro JP, Steiner TS, Guerrant RL. Enteroaggregative Escherichia coli (EAEC): an emerging cause of diarrhea and malnutrition. *Emerg Infect Dis*. 1998;4:251–261.
32. Wanke CA, Mayer H, Weber R, et al. Enteroaggregative Escherichia coli as a potential cause of diarrheal disease in adults infected with human immunodeficiency virus. *J Infect Dis*. 1998;178:185–190.
33. Wanke CA, Gerrior J, Blais V, et al. Successful treatment of diarrheal disease associated with enteroaggregative E. coli in adults infected with human immunodeficiency virus. *J Infect Dis*. 1998;178:1369–1372.
34. Huang RS, Johnson CL, Pritchard L, et al. Performance of the Verigene® enteric pathogens test, Biofire FilmArray™ gastrointestinal panel and Luminex xTAG® gastrointestinal pathogen panel for detection of common enteric pathogens. *Diagn Microbiol Infect Dis*. 2016;86:336–339.
35. Andersson AF, Lindberg M, Jakobsson H, et al. Comparative analysis of human gut microbiota by barcoded pyrosequencing. *PLoS ONE*. 2008;3:e2836.
36. Steiner TS, Lima AM, Nataro JP, et al. Enteroaggregative Esch-erichia coli produce intestinal inflammation and growth impairment and cause interleukin-8 release from intestinal epithelial cells. *J Infect Dis*. 1998;177:88–96.
37. Wanke CA, Cronan S, Goss C, et al. Characterization of binding of Escherichia coli strains which are enteropathogens to small-bowel mucin. *Infect Immun*. 1990;58:794–800.
38. Ramakrishna BS, Mathan VI. Role of bacterial toxins, bile acids, and free fatty acids in colonic water malabsorption in tropical sprue. *Dig Dis Sci*. 1987;32:500–505.
39. Malik AK, Mehta SK, Chandrashekhar Y, et al. Quantitation of immunoglobin-containing cells in the jejunal lamina propria in tropical sprue. *J Clin Gastroenterol*. 1992;14:163–166.
40. Marsh MN. Functional and structural aspects of the epithelial lymphocyte, with implications for coeliac disease and tropical sprue. *Scand J Gastroenterol*. 1985;115:55–75.
41. Marsh MN, Mathan M, Mathan VI. Studies of intestinal lymphoid tissue, VII. The secondary nature of lymphoid cell "activation" in the jejunal lesion of tropical sprue. *Am J Pathol*. 1983;112:302–312.
42. Tiruppathi C, Balasubramanian KA, Hill PG, et al. Faecal free fatty acids in tropical sprue and their possible role in the production of diarrhoea by inhibition of ATPases. *Gut*. 1983;24:300–305.
43. Glynn J. Tropical sprue: its aetiology and pathogenesis. *J R Soc Med*. 1986;79:599–606.
44. Cook GC. Aetiology and pathogenesis of postinfective tropical malabsorption (tropical sprue). *Lancet*. 1984;1:721–723.
45. Ghoshal UC, Kumar S, Misra A, et al. Pathogenesis of tropical sprue: a pilot study of antroduodenal manometry, duodenocaecal transit time and fate induced ileal break. *Indian J Med Res*. 2013;137:63–72.
46. Ramakrishna BS, Mathan VI. Absorption of water and sodium and activity of adenosine triphosphatases in the rectal mucosa in tropical sprue. *Gut*. 1988;29:665–668.
47. Lucas ML, Mathan VI. Jejunal surface pH measurements in tropical sprue. *Trans R Soc Trop Med Hyg*. 1989;83:138–142.
48. Kesavan V, Noronha JM. An ATPase-dependent, radiosensitive, acidic microclimate essential for folate absorption. *J Physiol*. 1978;280:1–7.
49. Davidson GP, Townley RRW. Structural and functional abnormalities of the small bowel due to nutritional folate deficiency in infancy. *J Pediatr*. 1977;90:590–594.
50. Morales M, Galván E, Mery CM, et al. Exocrine pancreatic insufficiency in tropical sprue. *Digestion*. 2001;63:30–34.
51. Tompkins A. Tropical malabsorption: recent concepts in pathogenesis and nutritional significance. *Clin Sci*. 1981;60:131–137.
52. Rolston DDK, Mathan VI. Jejunal and ileal glucose-stimulated water and sodium absorption in tropical enteropathy: implications for oral rehydration therapy. *Digestion*. 1990;46:55–60.
53. Batt RM, Bush BM, Peters TJ. Subcellular biochemical studies of a naturally occurring enteropathy in the dog resembling chronic tropical sprue in human beings. *Am J Vet Res*. 1993;44:1492–1496.
54. Cook GC, Menzies IS. Intestinal absorption and unmediated permeation of sugars in post-infective tropical malabsorption (tropical sprue). *Digestion*. 1986;33:109–116.
55. Westergaard H. The sprue syndromes. *Am J Med Sci*. 1985;290:249–262.
56. Besterman HS, Cook GC, Sarson DL, et al. Gut hormones in tropical malabsorption. *BMJ*. 1979;1252–1255.
57. Cook GC. Delayed small-intestinal transit in tropical malabsorption. *BMJ*. 1978;2:238–240.
58. Jayanthi V, Chacko A, Gani IK, et al. Intestinal transit in healthy southern Indian subjects and in patients with tropical sprue. *Gut*. 1989;30:35–38.
59. Wheby MS, Bayless T. Intrinsic factor in tropical sprue. *Blood*. 1968;31:817–820.
60. Ramakrishna BS, Mathan VI. Water and electrolyte absorption by the colon in tropical sprue. *Gut*. 1982;23:843–846.
61. Tawil SC, Brandt LJ, Bernstein LH. Scalloping of the valvulae conniventes and mosaic mucosa in tropical sprue. *Gastroenterology*. 1991;37:365–366.
62. Westergaard H. Tropical sprue. *Curr Treat Options Gastroenterol*. 2004;7:7–11.
63. Mathan MM, Ponniah J, Mathan VI. Epithelial cell renewal and turnover and relationship to morphologic abnormalities in jejunal mucosa in tropical sprue. *Dig Dis Sci*. 1986;31:586–592.
64. Gordon JI, Dewey KG, Mills DA, et al. The human gut microbiota and undernutrition. *Sci Transl Med*. 2012;4:137ps112.
65. Semba RD, Trehan I, Li X, et al. Environmental enteric dysfunction is associated with carnitine deficiency and altered fatty acid oxidation. *EBioMedicine*. 2017;17:57–66.
66. Semba RD, Gonzalez-Freire M, Moaddel R, et al. Environmental enteric dysfunction is associated with altered bile acid metabolism. *J Pediatr Gastroenterol Nutr*. 2017;64:536–540.
67. Thielman NM, Guerrant RL. An algorithmic approach to the workup and management of HIV-related diarrhea. *J Clin Outcomes Manag*. 1997;4:36–47.
68. Lo A, Guelrud M, Essenfeld H, et al. Classification of villous atrophy with enhanced magnification endoscopy in patients with celiac disease and tropical sprue. *Gastrointest Endosc*. 2007;66:382–386.
69. Campbell DI, Lunn PG, Elia M. Age-related association of small intestinal mucosal enteropathy with nutritional status in rural Gambian children. *Br J Nutr*. 2002;88:499–505.
70. Thompson AJ, Hughes M, Anastasova S, et al. Position paper: the potential role of optical biopsy in the study and diagnosis of environmental enteric dysfunction. *Nat Rev Gastroenterol Hepatol*. 2017;14:727–738.
71. Prata MM, Havt A, Bolick DT, et al. Comparisons between myeloperoxidase, lactoferrin, calprotectin and lipocalin-2, as fecal biomarkers of intestinal inflammation in malnourished children. *J Transl Sci*. 2016;2:134–139.
72. Ordiz MI, Wold K, Kaimila Y, et al. Detection and interpretation of fecal host mRNA in rural Malawian infants aged 6-12 months at risk for environmental enteric dysfunction. *Exp Biol Med (Maywood)*. 2018;243:985–989.
73. Ordiz MI, Shaikh N, Trehan I, et al. Environmental enteric dysfunction is associated with poor linear growth and can be identified by host fecal mRNAs. *J Pediatr Gastroenterol Nutr*. 2016;63:453–459.
74. Yu J, Ordiz MI, Stauber J, et al. Environmental enteric dysfunction includes a broad spectrum of inflammatory responses and epithelial repair processes. *Cell Mol Gastroenterol Hepatol*. 2016;2:158–174, e151.
75. Scully RE, Mark EJ, McNeely WF, et al. Weekly clinicopathologic exercises: case 15-1990. *N Engl J Med*. 1990;322:1067–1075.
76. Guerra R, Wheby MS, Bayless TM. Long-term antibiotic therapy in tropical sprue. *Ann Intern Med*. 1965;63:619–634.
77. Rickles FR, Klipstein FA, Tomasini J, et al. Long-term follow-up of antibiotic-treated tropical sprue. *Ann Intern Med*. 1972;76:203–210.
78. Gerson CD, Kent TH, Saha JR, et al. Recovery of small-intestinal structure and function after residence in the tropics, II. Studies in Indians and Pakistanis living in New York City. *Ann Intern Med*. 1971;75:41–48.
79. Maldonado N, Horta E, Guerra R, et al. Poorly absorbed sulfonamides in the treatment of tropical sprue. *Gastroenterology*. 1969;57:559–568.
80. Grassly NC, Praharaj I, Babji S, et al. The effect of azithromycin on the immunogenicity of oral poliovirus vaccine: a double-blind randomised placebo-controlled trial in seronegative Indian infants. *Lancet Infect Dis*. 2016;16:905–914.
81. Dangour AD, Watson L, Cumming O, et al. Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children. *Cochrane Database Syst Rev*. 2013;(8):CD009382.

K Bone and Joint Infections

103 Infectious Arthritis of Native Joints

Christopher A. Ohl

SHORT VIEW SUMMARY

DEFINITION

- Infectious arthritis is an infection of one or more joints that can be caused by bacteria, viruses, fungi, and parasites.

CLINICAL CATEGORIES

Acute Bacterial Arthritis

- Overall incidence in native joints is 2 to 12 per 100,000 per year, increased in rheumatoid arthritis (RA) and the elderly. Joint infections in persons who use intravenous (IV) drugs began to increase during the opioid abuse epidemic beginning in 2010.
- Infection is usually acquired from hematogenous dissemination, less commonly from direct joint inoculation, or from a contiguous focus. Most infections are monoarticular; 10% to 20% are polyarticular. The knee is most often involved.
- Microbiology
  - Gram-positive organisms, including *Staphylococcus aureus* and *Streptococcus* spp. predominate.
  - Gram-negative bacilli in 5% to 20% are mainly in neonates, the elderly, IV drug users, and the immunocompromised.
  - Prevalence rates of gonococcal arthritis have decreased. There are two syndromes of joint involvement: monoarticular arthritis and disseminated gonorrhea with febrile tenosynovitis and skin lesions.

Viral Arthritis

- It may occur sporadically or in community outbreaks that may be small (e.g., parvovirus B19) or explosive (e.g., chikungunya virus).
- It is caused by infection of the joint space or by immune-mediated inflammation.
- It is usually an acute symmetrical polyarticular arthritis that occurs simultaneously with other systemic symptoms of viral infection.
- Causes include parvovirus B19, chikungunya virus, rubella (which may follow immunization), hepatitis B, hepatitis C, and other viruses, including Ross River virus and o'nyong-nyong virus.
- Parvovirus B19 and chikungunya virus, in particular, may cause prolonged or chronic arthritis after acute infection.

Chronic Infectious Arthritis

- It is usually monoarticular, involving the large peripheral joints.
- It is relatively uncommon compared with acute bacterial arthritis but is increasingly seen in immunocompromised or chronically ill hosts. Etiology includes *Mycobacterium tuberculosis* and nontuberculous mycobacteria. Fungal causes include *Candida,* dimorphic fungi (e.g., *Blastomyces, Coccidioides,* and *Sporothrix*), rarely *Cryptococcus,* and molds, among others.

CLINICAL EVALUATION

- Bacterial arthritis is an emergency and should be considered in any patient with acute monoarticular arthritis and in bacteremic patients with oligoarticular joint inflammation.
- The most useful demographic risk factors are presence or absence of recent joint surgery, RA, advanced age, IV drug use, concomitant skin infection, or diabetes mellitus.
- The most helpful laboratory parameters are the synovial fluid leukocyte count and differential and examination for crystals to evaluate for gout or pseudogout.
- In patients with acute monoarticular arthritis an elevated serum procalcitonin can be predictive of bacterial joint infection.
- Diagnostic imaging should include plain film radiography. For prolonged or atypical symptoms or for deep joints, computed tomography or magnetic resonance imaging is recommended.
- Differential diagnosis includes crystalline, reactive, or traumatic arthritis, in addition to other monoarticular rheumatologic disorders.
- Identification of the infecting organism on synovial fluid Gram stain and culture remains the definitive diagnostic test. The polymerase chain reaction (PCR) assay continues to show promise.
- For gonococcal arthritis, testing should include nucleic acid amplification testing of cervical or vaginal and male urethral mucosa or urine.

THERAPY

Acute Bacterial Arthritis

- Joint drainage by repeat aspiration, arthroscopy, or arthrotomy is required.
- Empirical antibiotic selection should be based on synovial fluid Gram stain (see Table 103.5).
- IV therapy, in some instances with an oral transition, is usually prescribed for a total of 2 to 4 weeks.

Chronic Arthritis

- Therapy of *M. tuberculosis* arthritis is similar to pulmonary tuberculosis.
- Many fungal arthritides are difficult to treat and result in chronic joint disability. Treatment varies by infecting organism. Experience using the azoles (including new triazoles) and the echinocandins is growing, and in many cases these drugs are replacing amphotericin.
- Except for *Cryptococcus* and perhaps *Coccidioides* or *Sporothrix,* fungal arthritis requires surgical drainage and débridement.

SEPTIC BURSITIS

- It predominantly involves the prepatellar, olecranon, and trochanteric bursa.
- It can be caused by direct inoculation, contiguous infection, or, less commonly, from a hematogenous source.
- More than 80% of cases are due to *S. aureus.*
- Diagnosis is made from the clinical presentation and by aspirating the bursa for fluid analysis, Gram stain, and culture.
- Treatment includes antibiotics (usually 14–21 days) and daily aspiration of the bursa until sterile fluid is obtained. Surgery is rarely required. Except for severe cases, oral antistaphylococcal agents that have activity against community-acquired methicillin-resistant *S. aureus* are recommended, pending culture and sensitivity. For moderate-to-severe cases or patients with immunosuppression, intravenous (IV) antibiotics should be selected.

Infectious arthritis of single or multiple joints may be caused by any of a number of diverse microorganisms. Bacterial arthritis, also known as *suppurative, pyogenic,* or *septic arthritis,* is the most common and arguably most important joint infection and is considered a rheumatologic emergency because of its potential for rapid joint destruction with irreversible loss of function. Viral arthritis often involves multiple joints as a component of a systemic infection, and although usually self-limited, it may rarely lead to a chronic polyarticular arthritis. In contrast to the acute occurrence of bacterial and viral arthritis, joint infection caused by mycobacteria and non-*Candida* fungi usually occurs as chronic, slowly progressive monoarticular arthritis. Reactive arthritis (formerly Reiter syndrome), a sterile inflammatory spondyloarthropathy, is occasionally associated with systemic or local infection at a site remote to the joint rather than from direct infection of joint tissue. The clinical manifestations, severity, treatment, and prognosis of septic arthritis are dependent on the identity and virulence of the infecting bacterium, source of joint infection, and certain underlying host factors, such as immune status, comorbid illness, and abnormal joint architecture from disease or surgery. For patients with infectious arthritis a prompt and thorough clinical evaluation and early institution of specific treatment are essential to limit long-term sequelae.

This chapter will primarily discuss infections of native joints. For a detailed discussion of infections involving prosthetic arthroplasty see Chapter 105. Lyme arthritis caused by disseminated *Borrelia burgdorferi* (Lyme disease) infection is covered in Chapter 241.

ACUTE BACTERIAL ARTHRITIS

Epidemiology

The reported incidence of native joint septic arthritis in the general population of western Europe and the United States is between 2 and 12 cases per 100,000 per year.[1–5] Rates are increasing, particularly in the elderly, because of a larger number of at-risk patients and surgical joint procedures in recent years.[4–6] Estimates of the incidence in elderly patients and those with RA are much higher, ranging from 28 to 70 cases per 100,000 per year.[4–7] Although not well studied, socioeconomically disadvantaged populations appear to have a higher prevalence than the general population.[3,8] Bacterial arthritis is an uncommon but not rare diagnosis in the emergency department, accounting for 8% to 27% of patients presenting with one or more acutely painful joints.[9,10] Information on the epidemiology of septic arthritis is limited by the retrospective nature and varying case definitions used for many of the studies and the lack of a reliable gold standard for the diagnosis.

The published mortality rates of bacterial arthritis in adults vary between 7% and 15% but may be as high as 30% to 50% in those with significant comorbidity or multiple joint involvement.[3,11–15] Moreover, bone and joint infections that develop in a health care setting are associated with a significantly higher mortality rate, longer length of hospital stay, and greater financial cost than infections acquired in the community.[16] The morbidity of septic arthritis is considerable, with up to 50% of patients reporting permanent decreased joint function or mobility after infection, depending on the presence or absence of preexisting joint disease and identity of the infecting pathogen.[13,17,18] Despite improved antimicrobial agents and adjunct treatment measures, as well as advances in hospital care, the morbidity and mortality of septic arthritis has not changed appreciably in the past 2 to 3 decades.

Route of Infection

Bacterial arthritis is usually hematogenously acquired during overt or occult bacteremia, including that caused by endocarditis.[8,18–20] A study from Spain of cases from 1985–2011 of bacteremic osteoarticular infection noted an increase in cases, with an increased proportion of health care–related cases. Patients increasingly were found to be older, comorbidities were more common, and more cases were device related.[21] Normal, diseased, and prosthetic joints are all susceptible to hematogenous infection, although abnormal joint architecture greatly increases the risk. Thus patients with osteoarthritis, gout, and pseudogout are all at an increased risk of infectious arthritis.[5,22] The extremely vascular synovial membrane of the joint lacks a limiting basement membrane and is particularly susceptible to the hematogenous deposition of bacteria.[2,18,23] Most nosocomial cases of acute bacterial arthritis presumably occur via this route.[15,24]

Other routes of infection include direct inoculation of bacteria into the joint through surgery, trauma, animal and human bites, percutaneous puncture (such as from a nail, needle, or thorn), or from contiguous spread from adjacent infected soft tissue or bone.[2,8] A common example of the latter is septic arthritis of the small joints of the foot, complicating an adjoining diabetic foot ulcer or infection.[25] On occasion, hip joint infection may occur from contiguous spread from an intraabdominal source via the retroperitoneal space and iliac acetabulum.[26,27]

Septic arthritis is an unusual complication of arthroscopic surgical procedures of the knee, occurring in only 0.04% to 0.7% of arthroscopies and 0.14% to 2.3% of arthroscopic reconstructive procedures.[28–30] The incidence of infection after arthroscopic surgery of the shoulder may be somewhat higher, with one study reporting rates of 8.5 per 1000 rotator cuff repairs.[31] Similarly, it is also extremely rare for infection to follow a single joint aspiration or corticosteroid injection, occurring in less than 0.04% of those procedures.[5,32] Iatrogenic infections that follow joint corticosteroid injection may be caused by unusual pathogens and can occur in outbreaks or clusters related to contaminated medication, usually methylprednisolone.[33,34]

Predisposing Host Factors

Predisposing host factors for septic arthritis are listed in Table 103.1. The most important risk factor is preexisting abnormal joint architecture, particularly that caused by RA. A prospective cohort study of patients presenting with acute inflammatory arthritis found that recent joint surgery, age older than 80 years, diabetes mellitus, and RA were associated with a significant and increased incidence of septic arthritis (likelihood ratios: 6.9, 3.5, 2.7, and 2.5, respectively).[1] Prevalence was also increased for patients on hemodialysis in one study, although some of this risk was likely due to preexisting joint disease.[35] The immunosuppressive disease-modifying antirheumatic drugs (DMARDs) penicillamine, sulfasalazine, and prednisone have been identified to further increase the risk in patients with RA.[7,36] Although methotrexate therapy was found to be associated with septic arthritis in one investigation,[7] it was not so identified in a large retrospective controlled study.[36] Similarly, patients treated with anti–tumor necrosis factor (TNF) agents have increased risk for several infections, including those of the joint.[36–41] A

TABLE 103.1 Predisposing Factors in Bacterial Arthritis

Major Factors
Rheumatoid arthritis
Crystal induced arthritis (gout and pseudogout)
Advanced age
Diabetes mellitus
Chronic renal failure
Previous joint surgery
Penetrating joint injury
Intravenous drug use
Endocarditis
Immunosuppression
Organ and bone marrow transplant
Immunosuppressant therapy, including systemic corticosteroids, DMARDs, and anti-TNF agents
Minor Factors
Other joint disease
Osteoarthritis
Charcot arthropathy
Chronic systemic disease
Collagen vascular disease
Malignancy
Chronic liver disease
Sickle cell disease
Alcoholism
Hypogammaglobulinemia
Intraarticular injection (e.g., glucocorticoids)
Skin disease with or without infection
Low socioeconomic status

DMARDs, Disease-modifying antirheumatic drugs; *TNF,* tumor necrosis factor.
Data from references 1–5, 11, 20, 22, 32, 33, 41, 44, and 91.

large prospective observational study found that anti-TNF therapy doubled the risk (adjusted hazard ratio, 2.3) of septic arthritis in patients with RA. The risk was greatest in the first year of therapy and was not significantly different between the specific anti-TNF agents.[42] Moreover, opportunistic and intracellular pathogens are more likely to cause joint infections in these patients.

Regarding human immunodeficiency virus (HIV) infection, one study in Africa suggested that such patients may have a small increased risk for septic arthritis,[43] whereas other studies have found no such association.[44,45] The perceived increased risk in patients with HIV is likely related to concomitant IV drug abuse, an established risk factor for joint infection.[46,47] An important source of hematogenously derived joint sepsis is skin disease or lesions, with or without concurrent infection.[1,2] Of importance, up to 22% of patients with septic arthritis will not have an identifiable predisposing risk factor, and the negative predictive value of any one factor for joint infection is low. Thus the diagnosis must be considered in all persons presenting with inflammatory arthritis, even when risk factors are absent.[12,48,49]

Nongonococcal Arthritis

Pathophysiology

The pathophysiology of acute nongonococcal septic arthritis is complex and dependent on adherence of organisms to, and colonization of, the synovial membrane, bacterial proliferation in synovial fluid, and a resultant synovial infection with generation of a host inflammatory response.[50] Much of our understanding of these pathophysiologic mechanisms comes from studies of animal models of joint infection, particularly with *Staphylococcus aureus*.[51] After hematogenous or direct entry to the joint, bacterial adherence is facilitated by the low shear conditions of synovial fluid, and, in some cases, by joint disease or injury (traumatic or surgical). The later results in an increased amount or exposure of host-derived extracellular matrix proteins, such as fibronectin, collagen, laminin, elastin, and hyaluronic acid, which promote bacterial attachment.[23,52]

Some bacteria display a tropism for synovial infection, at least in part because of adherence characteristics of the organism. For example, *S. aureus* has surface receptors, such as fibronectin-binding protein and "microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs), that recognize selected host proteins and mediate adherence to the joint extracellular matrix (see Chapter 194).[53,54] Expression of these surface receptors, as well as several other virulence factors, are influenced by genes, including those regulating quorum sensing, which promote *S. aureus* invasion and infection when host defenses are weakened.[55,56] In the case of *Kingella kingae* and *Streptococcus agalactiae*, joint tropism and synovial adherence is influenced by bacterial pili and fibrinogen-binding adhesin proteins, respectively.[52,57]

Although certain bacterial products or toxins may directly increase tissue damage in the infected joint,[23,58–61] it is the host inflammatory response to infection that is responsible for much of the joint injury.[62,63] In response to replicating bacteria and a number of bacterial products an inflammatory cell response is rapidly noted within the joint synovial membrane, which then responds with a proliferative lining-cell hyperplasia.[64] An influx of acute and chronic inflammatory cells results in the characteristic purulent inflammation of the joint and its synovial fluid. Leukocyte-derived proteases and inflammatory cytokines, including interleukin-1 (IL-1), IL-4, IL-6, IL-10, and TNF-α, either directly or indirectly result in cartilage degradation, inhibition of cartilage synthesis, and subchondral bone loss.[23,24,63,65] Intraarticular cartilage destruction may be seen in as little as 3 days.[66] In addition, the inflammatory joint infusion increases intraarticular pressure, hampering capillary blood flow to the joint, resulting in cartilage and synovial ischemia and necrosis.[18] Over time cartilage destruction leads to joint space narrowing and further erosive damage to the cartilage and underlying bone. If untreated, infection can spread from the joint to surrounding soft tissue, disrupting ligaments, tendons, and other periarticular structures and occasionally forming sinus tracts.[67,68]

Microbiology

Septic arthritis is caused by a multitude of pathogenic bacteria (Table 103.2). Except for slight decreases in the proportion of cases due to gonococci, group A streptococci, and *Streptococcus pneumoniae,* and a modest increase due to *S. agalactiae*, the distribution of bacterial organisms causing septic arthritis has changed little over time.[2–6,12,25,69–73]

TABLE 103.2 Bacteria Isolated in 2302 Compiled Cases of Bacterial Septic Arthritis in Adults

ORGANISM	NO. OF ISOLATES (% OF TOTAL)
Gram positive	
Staphylococcus aureus	1066 (46)
Staphylococci, coagulase negative	84 (4)
Streptococci	512 (22)
Streptococcus pyogenes	183 (8)
Streptococcus pneumoniae	156 (7)
Streptococcus agalactiae	69 (3)
Other streptococci	104 (5)
Gram negative	
Escherichia coli	91 (4)
Haemophilus influenzae	104 (5)
Neisseria gonorrhoeae	77 (3)
Neisseria meningitidis	28 (1)
Pseudomonas aeruginosa	36 (2)
Salmonella spp.	25 (1)
Other gram-negative rods	110 (5)
Miscellaneous (including anaerobes)	136 (6)
Polymicrobial	33 (1)

Modified from Ross JJ, Saltzman CL, Carling P, et al. Pneumococcal septic arthritis: review of 190 cases. Clin Infect Dis. *2003;36:319–327.*

Gram-Positive Bacteria

By far, the most common etiology of septic arthritis in adults is *S. aureus,* which is responsible for 37% to 65% of cases, depending on geographic location, incidence of comorbid rheumatic disease, and proportion of infections involving native joints. For patients with RA the proportion of septic arthritis caused by *S. aureus* has been reported to be higher (≈75%).[67,74] In many geographic locations the incidence of methicillin-resistant *S. aureus* (MRSA) septic arthritis has increased compared with that in the 1990s, particularly in the elderly, persons with recent orthopedic surgery, and those colonized or previously infected by MRSA.[15,16,75–79] However, some studies, particularly those from western Europe, have not noted this increase, and others have reported little change in the proportion of joint infections due to MRSA since 2000.[25,73,80] Coincident with the increased prevalence of invasive infections caused by community-acquired MRSA (CA-MRSA) since 2003, there have been several reports of native joint infection caused by this pathogen, especially in children.[16,80–86] Septic arthritis caused by CA-MRSA is associated with increased morbidity, suppurative complications, and duration of fever, antibiotics, and hospitalization, compared with that caused by methicillin-susceptible *S. aureus* (MSSA).[81,82,87] Vancomycin-intermediate, but not high-level, resistantance in *S. aureus* has rarely been reported as a cause of septic arthritis in patients with frequent exposure to health care facilities.[86,88–90] Coagulase-negative staphylococci, a common pathogen in prosthetic joint infections, are rarely a cause of native joint septic arthritis. If isolated, however, it is important to differentiate *Staphylococcus lugdunensis* from other coagulase-negative staphylococci because of its increased virulence and propensity to cause invasive infections of native tissues.[91]

Streptococcus spp. are the next most frequently isolated bacteria from adults with native joint septic arthritis.[4–6,23,25,69–73] *Streptococcus pyogenes* and other β-hemolytic streptococci from Lancefield groups C, F, and G are important pathogens within this group. *S. agalactiae* is a cause of bacterial arthritis in neonates, as well as adults with diabetes mellitus, malignancy, and genitourinary structural abnormalities, and it is prone to occur with polyarticular infection.[92–95] Population surveillance from 1995–2012 in California showed an increased incidence of septic arthritis due to this organism, with diabetes mellitus the most common underlying condition.[96] *S. pneumoniae*, traditionally thought of as a rare cause of hematogenous septic arthritis in the antibiotic era, accounted for 6% of cases in a comprehensive systematic review.[71] Polyarticular infection was frequent (36%), and many patients did not have prior or concurrent respiratory tract infection. Some studies have shown lower numbers of joint infections due to this organism, particularly in children, since the adoption

of pneumococcal conjugate vaccine.[5,6,87] Pneumococcal vaccination has, however, likely shifted the percentage of pneumococcal joint isolates from serotypes included in the vaccine to nonvaccine serotypes.

Other streptococci are a less frequent cause of septic arthritis. *Streptococcus suis*, an emerging zoonotic pathogen in China, Southeast Asia, and to a lesser extent in Europe, has been reported to cause septic arthritis in persons exposed to pigs or improperly cooked pork.[97,98] Another emerging pathogen, *Streptococcus iniae,* is associated with aquaculture fish and has occasionally been described as a cause of bacterial arthritis in fish handlers.[99] Native joint septic arthritis caused by viridans group streptococci is rare, in contrast to prosthetic joint infections, where it is a common pathogen.[100] Osteoarticular infections with the *Streptococcus bovis* group, most frequently *Streptococcus gallolyticus* subsp. *gallolyticus*, are often a manifestation of infectious endocarditis, and evaluation for endocarditis and colonic malignancy should be undertaken.[101]

Gram-Negative Bacteria

Gram-negative bacilli are cultured from approximately 5% to 20% of patients with bacterial arthritis, particularly from neonates, the elderly, IV drug users, and immunocompromised hosts.[5,6,23,73,102] The coliform bacteria are most commonly isolated from the elderly, immunocompromised, and comorbidly ill[2,25,70,72] and are increasingly found to be multidrug resistant.[103,104] *Pseudomonas aeruginosa* is an important pathogen in IV drug users and has also been described as a cause of iatrogenic septic arthritis after surgical procedures and intraarticular injections.[105,106] It has a particular affinity for fibrocartilaginous articular structures, such as the pubic symphysis and the sternoclavicular, sternochondral, and sacroiliac joints.[107–111] *Haemophilus influenzae*, once an important pathogen in young children, now rarely causes septic arthritis in populations where *H. influenzae* type b vaccine is widely used.[112] For children younger than 4 years, *K. kingae,* a resident of the normal oral flora, has replaced *H. influenzae* as the principal gram-negative cause of hematogenous bacterial arthritis.[113–117] Joint infection caused by *K. kingae* is often associated with stomatitis or upper respiratory tract infection and typically responds well to therapy with minimal articular or functional sequelae. Child-to-child transmission of this communicable bacterium occurs, and outbreaks of *K. kingae* osteoarticular infections in child care centers have been reported.[117–119]

Other Bacteria

Other nongonococcal bacteria identified in infected joints include corynebacteria, *Salmonella* spp., *Neisseria meningitidis*, *Listeria monocytogenes, Burkholderia cepacia, Burkholderia pseudomallei, Legionella* spp., and *Brucella* spp. Articular infection caused by anaerobic bacteria is rarely reported.[120] An important exception, however, is *Cutibacterium acnes* (formerly *Propionibacterium acnes*), which is often isolated from infected shoulder joints after arthroscopic or open surgery.[31,121,122]

Unusual bacterial pathogens causing contiguous septic arthritis after a dog or cat bite include *Pasteurella multocida* and *Capnocytophaga* spp., and in the case of a human bite, *Eikenella corrodens* and *Fusobacterium nucleatum*.[123–126] *Streptobacillus moniliformis*, a causative agent of rat-bite fever, is occasionally isolated from the blood or synovial fluid in patients with polyarticular arthritis after a rat bite.[127,128] *Pantoea agglomerans* is the most common bacteria cultured from infected joints after direct plant thorn injury.[129] Table 103.3 lists selected clinical and epidemiologic associations with septic arthritis and their likely causative bacteria.

Cultures of synovial fluid or blood from patients diagnosed with septic arthritis yield polymicrobial flora in up to 10% of cases.[25,70] Causes of bacterial arthritis in which a pathogen is not isolated from blood or joint fluid using conventional culture techniques are *Mycoplasma hominis, Ureaplasma urealyticum, B. burgdorferi,* and *Tropheryma whipplei* (Whipple disease).

TABLE 103.3 Clinical and Epidemiologic Features Associated With Selected Bacterial Causes of Septic Arthritis

CLINICAL OR EPIDEMIOLOGIC FEATURE	ETIOLOGIC AGENT
Rheumatoid arthritis	*Staphylococcus aureus*
Intravenous drug use	*S. aureus, Pseudomonas aeruginosa*
Diabetes, malignancy	*S. aureus, Streptococcus agalactiae*
Immunocompromised hosts	*S. aureus,* streptococci, enteric gram-negative bacilli, *Listeria monocytogenes*
Neonates, children younger than 4 yr	*S. agalactiae,* gram-negative bacilli, *Kingella kingae*
Young adults, menstruating females, associated skin lesions	*Neisseria gonorrhea*
Fibrocartilaginous joints (e.g., pubic symphysis)	*S. aureus, P. aeruginosa*
Postsurgical shoulder joint	*Cutibacterium acnes*
Cat or dog bite	*Pasteurella multocida, Capnocytophaga* spp., anaerobes
Human bite	*Eikenella corrodens,* anaerobes, other oral flora (e.g., viridans streptococci)
Rat bite	*Streptobacillus moniliformis*
Postpartum women	*Mycoplasma hominis*
Ingestion of unpasteurized dairy products, residents or travelers from endemic areas	*Brucella* spp.
Residents or travelers to Southeast Asia	*Burkholderia pseudomallei* (melioidosis), *Streptococcus suis*
After plant thorn injury	*Pantoea agglomerans, Nocardia* spp.

Clinical Manifestations

Joints Involved

Nongonococcal septic arthritis is monoarticular in 80% to 90% of cases, with the knee being the predominate site of infection in up to 50% of patients.[2,5,6,20,25,130–132] Other native joints that are frequently involved in adults include the hip, shoulder, wrist, and ankle. In children hip infections predominate.[2] Infections of the peripheral joints of the hands are unusual, except in the setting of trauma, particularly animal or human bites.[125] Septic arthritis of the small joints of the foot is most often secondary to contiguous spread from skin and soft tissue ulcerations or adjacent osteomyelitis and is mostly seen in diabetic patients.[25,133] Nongonococcal polyarticular bacterial arthritis is observed in 10% to 20% of patients with septic arthritis, especially in those with RA, immunosuppression, or prolonged or intense bacteremia that is often associated with endovascular infections and intravenous drug use (IVDU).[5,6,14] These infections are usually caused by *S. aureus*. Sternoclavicular or costochondral joint infections are uncommon except in IV drug users and occasionally as a complication of occult bacteremia or subclavian vein catheterization.[110,134,135] In these cases *P. aeruginosa* is a frequent pathogen. Risk factors for septic arthritis of the pubic symphysis include female urinary incontinence surgery, participation in athletics, pelvic malignancy, and IVDU.[109]

Sacroiliac joint infection is an uncommon metastatic complication of occult or symptomatic bacteremia, usually caused by *S. aureus*.[107,136–140] IV drug abusers and patients with indwelling catheters are at risk. Patients typically present with acute onset of sacral or pelvic pain and leukocytosis. Blood cultures are often positive. Patients should be evaluated for the presence of concomitant infective endocarditis. Uncommon causes include *Salmonella* spp., including *Salmonella enterica* serovar Typhi, and brucellosis.[137,141,142] Brucellosis causes a chronic unilateral infection of the sacroiliac joint that must be distinguished from arthritis associated with inflammatory bowel disease (IBD) and ankylosing spondylitis (see Chapter 226). Injection of contaminated methylprednisolone into the sacroiliac joint led to an indolent sacroiliac joint infection caused by *Exserohilum* during a multistate outbreak of meningitis, epidural abscess, and joint infection caused by this pathogen.[143]

Clinical Presentation

Most patients with acute bacterial arthritis present with the cardinal symptoms of arthritis—pain and loss of function of one or more joints

over a 1- to 2-week period. In addition to intense pain and decreased range of motion, other symptoms of nongonococcal bacterial arthritis include swelling, redness, and increased warmth of the infected joint.[3,6,12,18,24] Joint pain is often the only focal symptom of deep or axial joint infection. In the case of sacroiliac or pubic symphysis septic arthritis, pain is intensely exacerbated by ambulation and often radiates to the back or groin, respectively, and to the hip and proximal leg in either case.[107,109,144] Although fever and malaise are commonly associated with bacterial arthritis in adults, high fever with rigors and shaking chills are typically not apparent and may be totally absent in 30% to 50% of patients.[6,18,20,24] A systematic review showed that fever was present as a physical examination finding in approximately 50% of patients, and it was found to have a sensitivity for articular infection of only 57%.[48]

Physical examination findings of infected peripheral joints include focal joint tenderness, inflammation, and effusion (Fig. 103.1). Active and passive range of motion of the joint is usually limited and results in considerable discomfort. Examination findings in patients with bacterial arthritis of the nonperipheral joints may be limited to focal tenderness over the afflicted area. Children with septic arthritis of the hip characteristically hold the hip in a flexed and externally rotated position and resist any range of motion. Weight bearing is painful. A source of infection distant from the afflicted joint, including that of the skin, may be discovered after careful clinical evaluation in up to 50% of patients.[20]

Patients who are immunocompromised, have comorbid illnesses, including RA, or are at the extremes of age often present without a fever and with significantly more subtle symptoms and signs of joint infection, frequently resulting in delayed diagnosis.[3,4,102,130,145] For patients afflicted with RA or other chronic joint disease, particularly those receiving systemic or intraarticular steroids, manifestations of a complicating joint infection may be limited to a modest increase in the severity of chronic articular inflammation and loss of joint function. In these cases it can be very difficult to differentiate joint infection from an exacerbation of their underlying disease.[11,48,146]

FIG. 103.1 (A) Bacterial arthritis of the knee showing swelling and effusion. (B) Septic third proximal interphalangeal joint demonstrating striking redness, swelling, and effusion.

Laboratory Findings

Laboratory evaluation frequently shows an elevated peripheral white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP); however, these tests are nonspecific and, if elevated, do not appreciably raise the pretest probability of septic arthritis.[24,48,147,148] Similarly, a nonelevated ESR or CRP may be found in native joint infections due to low virulence organisms.[148,149] However, in one retrospective analysis of 17 cases, a CRP exceeding 10.5 mg/dL was considered predictive of septic arthritis.[147]

Serum procalcitonin (PCT), an acute-phase reactant more sensitive and specific than ESR and CRP, may potentially be useful for the diagnosis of acute bacterial arthritis.[150,151] PCT was evaluated in a meta-analysis for the identification of osteomyelitis and septic arthritis in patients who had fever and orthopedic symptoms. For those patients with septic arthritis, using a cutoff level of 0.5 ng/mL, the diagnostic sensitivity and specificity were 65% and 88%, respectively, and the positive and negative likelihood ratios were 5.3 and 0.4, respectively.[152] Adjusting the cutoff level for positivity gives modestly different performance characteristics, and there is no clear consensus as to the optimum value.[153] Thus an elevated serum PCT might help suggest bacterial septic arthritis in a patient with an acutely inflamed joint, but, more important, a normal value is not useful for ruling it out.[150,152,154]

Arthrocentesis of an affected joint usually reveals purulent, low-viscosity synovial fluid with an elevated polymorphonuclear neutrophil count. Traditionally, a synovial fluid leukocyte count greater than 50,000 cells/mm^3 has been used to suggest a diagnosis of septic arthritis[4,18]; however, lower WBC counts are regularly encountered and do not exclude the diagnosis (Table 103.4).[48] Synovial fluid WBC counts between 25,000 cells/mm^3 and 75,000 cells/mm^3 constitute a "gray zone" for the diagnosis of bacterial arthritis, and careful clinical assessment and observation is necessary in such patients.[155] Other potential tests of synovial fluid laboratory tests have been evaluated. Although synovial fluid glucose may be depressed and protein and lactate dehydrogenase elevated, the sensitivity and specificity of these tests are low and limit their usefulness.[48] The diagnostic accuracy of an elevated synovial fluid lactic acid, PCT, or an inflammatory cytokine, such as TNF-α, has not been adequately assessed.[24,48,152,156]

Microbiologic Diagnosis

Conventional culture. Synovial fluid culture in nongonococcal infection of patients who have not previously received antibiotics will yield bacterial growth up to 80% to 90% of the time; however, Gram staining is diagnostic in only 50% of these cases.[12,72,148] False-positive Gram stains of synovial fluid can occur because of artifacts from stain, mucin, and cellular debris. There is some evidence that direct inoculation of synovial fluid into pediatric or adult blood culture media bottles or isolator culture tubes improves the recovery of pathogens,[157,158] although one investigation comparing the BACTEC (Becton Dickinson, Franklin Lakes, NJ) blood culture bottle to lysis centrifugation and conventional agar plate culture techniques found similar yields from all three methods.[159] However, using a blood culture system for synovial fluid culture may enhance the yield of fastidious organisms, such as *K. kingae* and *Brucella* spp.[160,161] Synovial fluid cultures from potentially infected shoulders should be incubated for at least 10 days, to enhance the isolation of *C. acnes*, a slow-growing bacterium that is an important cause of infection of this joint.[162]

TABLE 103.4 Diagnostic Parameters of Synovial Fluid White Blood Cell Count and Percent Polymorphonuclear Cells in Patients With Septic Arthritis

			LIKELIHOOD RATIO (95% CI)	
	SENSITIVITY (%)	SPECIFICITY (%)	Positive	Negative
>100,000 WBC/mm^3	29	99	28.0 (12.0–66.0)	0.71 (0.64–0.79)
>50,000 WBC/mm^3	62	92	7.7 (5.7–11.0)	0.42 (0.34–0.51)
>25,000 WBC/mm^3	77	73	2.9 (2.5–3.4)	0.32 (0.23–0.43)
PMN cells ≥90%	73	79	3.4 (2.8–4.2)	0.34 (0.25–0.47)

CI, Confidence interval; *PMN,* polymorphonuclear; *WBC,* white blood cell.
Modified from Margaretten ME, Kohlwes J, Moore D, et al. Does this adult patient have septic arthritis? JAMA. *2007;297:1478–1488.*

The proportion of patients with positive blood cultures in nongonococcal bacterial arthritis varies from 25% to 70%, depending on the study.[12,20] Of note, they are the sole source of the infecting organism's identity in approximately 10% of cases. Both synovial fluid and blood culture sensitivity declines in patients after antimicrobial therapy has been initiated.

False-positive synovial fluid cultures due to bacterial contamination occasionally occur and are more likely in aspirates from the wrist and shoulder. Clinical features suggesting a false-positive culture include low synovial fluid WBC counts, isolation of coagulase-negative *Staphylococcus* or *Bacillus* spp., and time to positivity of more than 48 hours.[163] *C. acnes* can be especially problematic when isolated from a native or prosthetic shoulder joint. Although this organism is a significant cause of infection of this joint, false-positive cultures also occur. Growth of the organism after 9 days of incubation is more likely to be a culture contaminant; however, careful clinical correlation is essential before discounting it as a false-positive culture.[164]

Molecular tests. Identification of bacterial DNA in synovial fluid by multiplex or broad-range polymerase chain reaction (PCR) assay shows promise for improving the etiologic diagnosis of septic arthritis, especially for infections caused by fastidious or unusual pathogens.[165–168] Identification of *K. kingae*, *Streptococcus* spp., *Mycoplasma,* and anaerobic bacteria is particularly enhanced. One technique showed a sensitivity and specificity of 95% and 97%, respectively, by using a 16S ribosomal DNA (rDNA) gene target and real-time PCR.[166] The negative predictive value in a separate study was 98%.[169] Although PCR performance is generally thought to be high, one study comparing three 16S rDNA targets reported more modest results, with sensitivities of 44% to 63% and negative predictive values of 84% to 89%.[170] Another study using multiplex PCR testing reported a negative result by PCR for *S. aureus, S. pneumoniae,* and *S. dysgalactiae* despite positive synovial fluid cultures for these organisms.[171]

In addition to the identification of fastidious organisms, other benefits of PCR include rapid results, high negative predictive values, and greater likelihood of yielding a pathogen from patients who have previously received antibiotics. Limitations of PCR include false-positive tests as a result of sample contamination, lack of antimicrobial susceptibility data, and, in the case of broad-range PCR, difficulty in confirming a specific species because of shared regions of bacterial 16S DNA. A multicenter evaluation of multiplex PCR to assess for the presence of bacterial pathogens in synovial fluid is ongoing, and early results show promise.[172] Molecular testing as a tool for the diagnosis of septic arthritis is likely on the horizon.

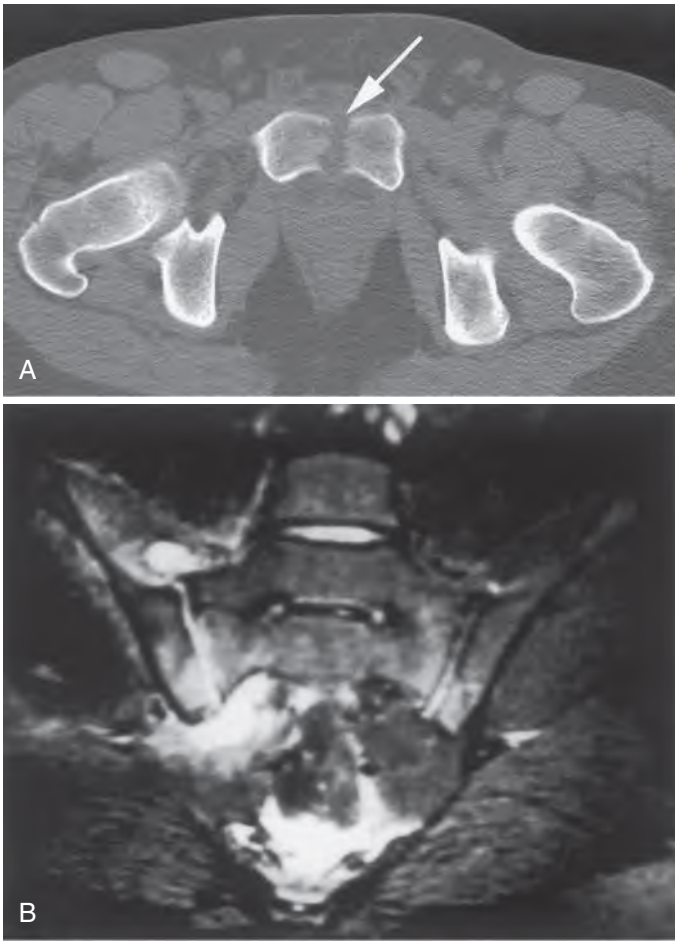

FIG. 103.2 (A) Septic arthritis of the symphysis pubis. Computed tomography of the pelvis reveals joint space widening *(arrow)* with subchondral bone resorption and disruption of the articular cortical margins. (B) Septic sacroiliac joint. Coronal T2-weighted magnetic resonance image demonstrates fluid within the right sacroiliac joint, spreading superiorly and inferiorly to form soft tissue abscesses. *(From Chew FS, Maldjian C, Leffler SG.* Musculoskeletal Imaging: A Teaching File*. Philadelphia: Lippincott Williams & Wilkins; 1999:267.)*

Radiographic Features

Imaging studies of joints and periarticular structures affected by bacterial arthritis often yield additional information helpful for establishing the diagnosis or evaluating for complications of infection.[173] Plain film radiography in early infection will typically show periarticular soft tissue swelling and fat-pad edema but normal osseous structures.[174] In advanced infection findings may include periarticular osteoporosis, joint space loss, periosteal reaction, marginal and central erosions, and destruction of subchondral bone. Plain films are useful for assessment of preexisting joint disease, metallic foreign bodies, and simultaneous osteomyelitis, or as a baseline image in monitoring for sequelae of infection.

Scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are highly sensitive techniques for imaging early septic arthritis. Scintigraphy, including three- or four-phase bone scanning, using technetium 99m methylene diphosphonate, are sensitive but nonspecific indicators of articular infection.[174] CT is useful for the detection of erosive bone changes, subchondral cysts, joint effusions, and periarticular soft tissue extension of infection, particularly in deep articulations, such as the hip, sacroiliac, and sternoclavicular joints and in the pubic symphysis (Fig. 103.2).[109,144,174–176]

Similar to bone scanning and CT, MRI is an extremely sensitive procedure for the evaluation of bacterial arthritis but is more specific than these other modalities.[177,178] MRI is particularly valuable for the detection of joint inflammation, effusion, and articular cartilage destruction, as well as for periarticular cellulitis, fistula, abscess, or osteomyelitis of contiguous bone. In some cases findings on MRI may discriminate between septic arthritis and underlying chronic RA.[179] However, MRI may pose difficulties distinguishing septic arthritis from sterile inflammatory arthropathies, cannot be used with certain metal joint implants, and has lower resolution for the bony cortex than CT.[23,177] Dynamic contrast-enhanced MRI, a technique that has shown usefulness in differentiating septic arthritis and transient tenosynovitis involving the hip joint, may also have use for evaluation of other joints.[180] In most US medical centers, MRI and CT have replaced scintigraphy as the preferred imaging modalities for evaluation of a potentially infected joint.

Particularly in children, sonography of the hip can provide rapid evidence of effusion and can guide prompt joint aspiration without waiting for advanced imaging.[173,181]

Gonococcal Arthritis

Epidemiology

During the 1970s and 1980s, *Neisseria gonorrhoeae* was the predominant cause of bacterial arthritis in sexually active adults and adolescents, with the majority of cases occurring in persons younger than 30 years.[182,183] Of note, the prevalence of gonococcal arthritis markedly declined as the rate of mucosal gonorrhea decreased fivefold between 1975 and 2011 to one of the lowest rates since statistics have been recorded.[184] Since 2011, however, rates of mucosal gonorrhea has rebounded, and consequently the prevalence of gonococcal arthritis has likely followed this increase.[185]

Gonococcal arthritis is one of two clinical manifestations of disseminated gonococcal infection (DGI), the other being a syndrome of tenosynovitis, dermatitis, and polyarthralgia without purulent joint infection.[182,186] There is overlap between the two conditions, and in some patients disseminated infection may progress from a bacteremic tenosynovitis-dermatitis syndrome to localized joint infection. Septic monoarticular or oligoarticular arthritis occurs in 42% to 85% of patients with disseminated gonococcal infection.[187]

DGI is usually diagnosed in persons younger than 40 years, is approximately four times more common in women than men, and complicates 0.5% to 3% of persons with mucosal gonococcal infection.[182,188] More recently the proportion of cases occurring in men is likely increasing due to the increasing percentage of mucosal infection in men with HIV and men who have sex with men (MSM).[185,189] Epidemiologic characteristics associated with DGI consist of lower socioeconomic status, nonwhite ethnicity, MSM, multiple sexual partners, and illicit drug use.[186] The incidence is markedly less in Europe than in North America, and it is considerably higher in the developing world.[182]

Pathogenesis

Gonococcal arthritis and DGI occur as a result of occult bacteremia secondary to mucosal infection of the urethra, uterine cervix, rectum, or oropharynx. Asymptomatic mucosal infection is much more likely to result in DGI than symptomatic infection and may have been sexually contracted days to months before dissemination. This, at least in part, accounts for the increased risk of disease in women for whom endocervical gonorrhea may persist without symptoms for extended periods. For these women the risk of DGI increases substantially during menstruation, pregnancy, and the direct postpartum period. One-third to one-half of all women who present with DGI will do so during these times.[187,190,191] Other host factors that increase the risk of DGI are complement deficiencies, particularly the terminal components C5 to C8,[192–195] and systemic lupus erythematosus.[196] Patients receiving eculizumab, a monoclonal antibody that inhibits terminal complement activation and thus increases risk for *Neisseria meningitidis* infection, also appear to be at higher risk for DGI.[197] Immune mechanisms, including circulating immune complexes, also likely play a part in the pathogenesis of DGI and gonococcal arthritis and may account, in part, for the low yield of cultures for *N. gonorrhoeae* in synovial fluid and skin pustules.[183]

N. gonorrhoeae possesses several virulence factors, many of them cell surface proteins, that influence pathogenesis and the ability of the organism to widely disseminate from infected mucosa. Microbial attachment to mucosal and synovial epithelium is facilitated by long pili that also play a role in inhibiting host leukocyte phagocytosis.[198] Gonococcal strains with the ability to disseminate are serum resistant and almost always express protein 1A, a principal outer membrane protein.[188,199–201] Other characteristics of strains with an increased propensity to disseminate include lack of outer membrane protein II, also called "opacity protein," and nutritional requirements for arginine, hypoxanthine, and uracil.[23,182,202] *N. gonorrhoeae* strains that cause DGI are resistant to the bactericidal effects of normal human serum, probably through changes in cell membrane lipooligosaccharide.[203]

Antimicrobial Resistance

N. gonorrhoeae displays acquired resistance to several antimicrobials, including β-lactams, tetracyclines, fluoroquinolones, and, rarely, spectinomycin.[204,205] The rapid emergence of fluoroquinolone resistance in *N. gonorrhoeae* throughout the world since 2001 has resulted in fluoroquinolones being contraindicated for empirical therapy of gonococcal infection.[204,206,207] In addition, minimal inhibitory concentrations (MICs) of the oral cephalosporin cefixime against *N. gonorrhoeae* from North America increased markedly between 2009 and 2011.[185] This, together with treatment failures using cefixime for gonococcal mucosal infections, led the Centers for Disease Control and Prevention (CDC) to no longer recommend this treatment for gonorrhea in 2010.[208,209] Amplifying the problem, MICs of azithromycin, the remaining oral drug with activity against *N. gonorrhoeae,* have also sharply increased. Between 2012 and 2017 the proportion of isolates resistant to azithromycin steadily increased from 0.3% to 4.4%.[185] In consequence, ceftriaxone the only antimicrobial with reliable activity against *N. gonorrhoeae*, is the remaining cornerstone for treatment of gonorrhea. Fortunately, in 2017 only 0.5% of isolates showed decreased susceptibility to this drug, and no isolates with elevated azithromycin MICs had elevated ceftriaxone MICs. Regrettably, precise epidemiologic data are not available on the antimicrobial susceptibility of strains of *N. gonorrhoeae* isolated from patients with DGI or gonococcal arthritis compared with strains from mucosal infections. This steady emergence of resistance of *N. gonorrhoeae* to numerous antimicrobials, particularly in the Pacific Rim and among MSM, has led to considerable concern that gonorrhea could soon attain an untreatable status.[209,210]

FIG. 103.3 Tenosynovitis of the dorsal hand accompanying monoarticular arthritis of the wrist. *Neisseria gonorrhoeae* was isolated from synovial fluid culture of the wrist.

Clinical Manifestations

Patients with DGI typically present with the classic triad of dermatitis, tenosynovitis, and migratory polyarthralgia or polyarthritis.[a] Joint symptoms may be quite severe and are often asymmetrical. Moderate fevers, chills, and general malaise are usually present. Two-thirds of patients develop tenosynovitis, usually occurring in the fingers, hands, and wrists, although the distal large and small joints of the lower limbs can also be involved (Fig. 103.3). The hip is rarely affected. Less than one-half of patients will have a true septic arthritis with a purulent joint effusion. The lesions of dermatitis are seen in two-thirds of DGI patients, are painless and nonpruritic, are few in number, and may not be noticed by the patient.[186,212] Macules, papules, and pustules on an erythematous base are most commonly seen and will often develop central necrosis (Fig. 103.4). The rash characteristically appears simultaneously with tenosynovitis and will be seen in various stages of development involving the limbs and hands (including the palms and soles), less often the torso, and rarely the face. Lesions will resolve after 4 to 5 days even if untreated, and new lesions may materialize after antimicrobial therapy is initiated.[186]

Septic gonococcal arthritis arising without tenosynovitis or skin lesions is less common than the so-called bacteremic form described previously and is clinically indistinguishable from bacterial arthritis caused by other organisms. The knees, wrists, and ankles are most commonly affected, and monoarthritis is more common than polyarthritis. Joints tend to be markedly inflamed, with large effusions. A syndrome of tenosynovitis with skin lesions may have occurred before the patient seeks medical care. Mucosal infection is usually present in patients with DGI and purulent gonococcal arthritis, although it is usually asymptomatic.

[a]References 183, 186, 187, 190, 196, 211.

FIG. 103.4 Pustular lesion overlying the fifth toe in a patient with disseminated gonococcal infection. *(Courtesy Graham International Dermatopathology Learning Center.)*

Laboratory Testing

As with nongonococcal septic arthritis, the laboratory findings of gonococcal arthritis and DGI include mild leukocytosis and elevated ESR in about 50% of patients.[186,187] Synovial fluid from joint effusions afflicted with gonococcal arthritis will frequently, but not invariably, have 50,000 to 100,000 WBCs/mm^3, predominantly neutrophils, whereas joint aspirates from patients with DGI without frank suppurative arthritis will exhibit lower cell counts.[186] *N. gonorrhoeae* is cultured from synovial fluid in approximately 50% of these cases and in 20% to 30% of patients with DGI.[182,186,187] Only 25% of Gram-stained joint aspirates from patients with suppurative gonococcal arthritis reveal intracellular and extracellular gram-negative diplococci. Significantly higher proportions of patients with DGI are found to have *N. gonorrhoeae* identified in synovial fluid by PCR assay than by conventional culture, with PCR assay sensitivity reported around 80%.[213–215] Synovial fluid PCR for *N. gonorrhoeae* is currently limited in most clinical laboratories but may be available in the near future.

For patients with DGI and gonococcal arthritis, culture yield of *N. gonorrhoeae* is much higher from mucosal sites than from synovial fluid or blood. Cultures are positive from uterine cervical swabs in 80% to 90% of women and from urethral swabs in 50% to 70% of men.[186,187,190] Culture yields from rectal and oropharyngeal swabs are lower but will sometimes give positive results. Positive blood cultures are exhibited by less than 30% of patients and are more common in those with dermatitis and tenosynovitis.[211,212,216] Gram staining and bacterial culture of skin lesions rarely yield organisms.

The use of nucleic acid amplification tests (NAATs) that are cleared by the US Food and Drug Administration (FDA) are now the recommended diagnostic testing modality for the detection of genital tract infection in women and men.[217] The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of other tests available for the diagnosis of gonococcal and chlamydial infections.[218,219] Thus a mucosal NAAT should be performed for anyone with suspected gonorrhea, DGI, and gonococcal septic arthritis.[217] Mucosal NAATs should be obtained from either a cervical or self-collected vaginal swab specimen in women and from a first-catch morning urine specimen in men. Gonococcal culture is still preferred for rectal and oropharyngeal specimens and should be done in addition to a NAAT for specimens from all sites when antimicrobial susceptibility testing is indicated (e.g., suspected treatment failure).[217]

Septic Arthritis in Persons Who Inject Drugs

IVDU and addiction have been well described for more than 50 years, but since 2010 it has become a significant public health crisis, particularly opioid use disorder (OUD). In 2016 11.8 million Americans were users of prescription opiates or IV heroin.[220] Concomitant with this outbreak of OUD, nonviral IVDU infections have increased markedly in persons who inject drugs (PWID), resulting in substantial morbidity, mortality, and increased hospitalizations in this population.[221] (See Chapter 312.)

Although accurate numbers are not available, bone and joint infection in PWID is common. Estimates of the proportion of all such infections presenting in either identified or later-identified PWID increased from 3% to 12% in 2000 to 11% to 15% in 2014 and was greater in younger age groups.[221,222] Up to half of all PWID-related joint infections may be in unrecognized users; thus there are opportunities to diagnose or treat underlying drug use in patients presenting with septic arthritis, particularly those who are of younger age.[221]

Morbidity, mortality and complications of hospitalization are higher for septic arthritis in PWID than in those who do not inject drugs. One report found an adjusted odds ratio for death during hospitalization of 2.86, and repeat arthroscopic or open débridement of 1.24 and 1.68, respectively. In addition, they were more likely to leave against medical advice and have an additional 5 days of hospital stay.[222]

The bacteria responsible for joint infections in PWID are acquired either from commensal flora from the user's skin or saliva or from organisms contaminating illicit drugs, drug diluents/adulterants, or paraphernalia.[223] Occult or overt bacteremia is the most common route for joint seeding. Although commensal skin flora is the most usual origin of pathogens, contaminated water is also a frequent source. Depending on the study, *S. aureus* accounts for 50% to 90% of joint infections with methicillin-resistant isolates accounting for 25% to 40% of these.[6,223–225] *S. aureus* and MRSA are isolated more commonly in PWID than in those who do not inject drugs. Other pathogens isolated from infected joints in PWID are similar to non-IVDUs, except for higher numbers of viridians streptococci, *Bacillus* spp., *P. aeruginosa*, *Serratia marcescens*, nonfermenting gram-negative rods, nontuberculous mycobacteria, and *Candida* spp. The microbiology of joint infections in PWID has not changed appreciably over the last 3 decades, except for increases in those due to MRSA.[6,224,225]

Similar to septic arthritis in non-IVDUs, the most common joints involved in septic arthritis in PWID are the knee, hip, shoulder, and wrist.[6,223,225] Joints that are rarely infected in non-IVDUs that are more commonly septic in PWID include the sternoclavicular, sacroiliac, pubic symphysis, and cervical facet joints.[223,226] Other notable clinical features of septic arthritis in PWID include more clinical presentations associated with endocarditis, bacteremia, sepsis, and polymicrobial joint infection.

Management

Initial Approach to the Patient

Patient Assessment

The diagnosis of bacterial arthritis is considered a rheumatologic emergency and should be considered in any patient with acute monoarticular or polyarticular arthritis. Septic arthritis of the hip in a child is an extreme emergency and should be treated in the first 6 to 12 hours.[181] Distinct features of the patient's demographics, clinical history, preexisting joint disease, comorbidity, physical examination, and initial laboratory and imaging may each raise the pretest probability of septic arthritis (see discussion in "Clinical Manifestations" under "Nongonococcal Arthritis"). A method for estimating the pretest probability of an infected joint has been suggested based on clinical risk factors that are identified in the evaluation of the patient with a painful swollen joint.[48] The most useful demographic risk factors are presence or absence of recent joint surgery, RA, advanced age, concurrent skin infection, or diabetes mellitus. The most helpful laboratory parameter is the synovial fluid leukocyte count and differential (see Table 103.4). If more than one factor is present, likelihood ratios from each are multiplicative rather than additive. Evidence-based guidelines for the diagnosis and management of septic arthritis have been published and were updated without changes in 2017 by the British Society for Rheumatology Standards, Guidelines and Audit Working Group.[227]

Laboratory Assessment

As part of the clinical assessment, routine laboratory tests should be drawn for identification of comorbid conditions and as a baseline for future antimicrobial monitoring. ESR, CRP, and PCT, although not often predictive for the diagnosis of septic arthritis, may be useful for assessing response to therapy or as a prognostic marker. Cultures should

be obtained from blood, any wound contiguous with the afflicted joint, and skin lesions if present. Plain film joint radiographs should be taken, and if there is concern for soft tissue or osseous extension of infection or prolonged or atypical joint symptoms, CT and MRI should be considered.

Synovial Fluid Assessment

Arthrocentesis should be performed on all patients with inflammatory arthritis in whom joint infection is within the differential diagnosis. Skin visibly involved with cellulitis should be avoided when entering the joint. For cases of polyarticular arthritis, multiple afflicted joints should be aspirated. For axial and deep joints that are difficult to aspirate at the bedside (e.g., sacroiliac or pubic symphysis) or in the event of a "dry tap" of a peripheral joint, fluoroscopic- or CT-guided arthrocentesis is indicated. Synovial fluid examination should include cell count, leukocyte differential, and crystal examination under polarized light. Tests that need not be performed because of limited utility include viscosity, total protein, lactate dehydrogenase, glucose, lactic acid, and bacterial capsular antigens. Gram stain and aerobic and anaerobic bacterial cultures should be performed. If blood culture bottles or isolator tubes are used, they should be inoculated at the bedside. In patients who are immunocompromised, or in cases with subacute, chronic, or relapsing presentation or penetrating joint trauma, fungal and mycobacterial smear and culture are indicated.[228] All cultures should be processed promptly in the laboratory. Antimicrobial therapy should be delayed until arthrocentesis and appropriate diagnostic cultures are obtained, unless the patient shows signs of sepsis. Orthopedic consultation is often necessary for joint drainage, irrigation, and débridement, and orthopedic or rheumatologic assistance is occasionally needed for diagnostic arthrocentesis.

Other Analysis

If gonococcal arthritis is suspected, NAATs for *N. gonorrhoeae* should be obtained from genitourinary sites and/or freshly voided urine, in addition to cultures from the rectum and oropharynx. Although NAATs alone will yield a diagnosis, it is extremely important that culture also be performed in cases that have relapsed or not responded to treatment to allow for antimicrobial sensitivities of an *N. gonorrhoeae* isolate. Because of the high frequency of antimicrobial-resistant gonococcal infections, knowledge of drug susceptibility is vital for guiding therapy in these cases.

Serology is occasionally helpful for diagnosis of nonbacterial joint infections. Serologic testing for *B. burgdorferi* is indicated for patients with clinical features of Lyme arthritis in endemic areas, especially if they are at risk for tick bites (see Chapter 241). Serology, and, if available, synovial fluid or peripheral blood PCR, may also be helpful in the diagnosis of the various viral arthritides, including parvovirus B19 and chikungunya.

Differential Diagnosis

Crystalline Arthritis

The differential diagnosis of pyogenic arthritis includes several inflammatory joint diseases caused by noninfectious sources, in addition to joint infections caused by nonbacterial pathogens. Acute attacks of the crystalline joint diseases, gout, and pseudogout are perhaps the greatest mimics of bacterial arthritis. There is significant overlap in the clinical findings of these two entities because both may occur with monoarticular symptoms of warmth, swelling, pain, and erythema of the involved joint. In addition, systemic signs of inflammation, including fever and elevations of peripheral WBC counts, are often evident. For patients with a history of gouty attacks in stereotypical joints, acute joint inflammation is more likely caused by crystalline than bacterial arthritis; however, in such attacks, arthrocentesis is necessary to rule out concomitant bacterial infection.

The coexistence of crystalline and bacterial arthritis is probably not as rare as previously thought.[229–232] One retrospective study found that, of 265 joint synovial fluid aspirates that contained crystals, 1.5% of the bacterial cultures were positive.[233] Of importance, the mean synovial WBC was significantly higher in the patients who had positive cultures compared with that of the entire study population (113,000 cells/mm^3 vs. 23,200 cells/mm^3). In another study of patients with septic arthritis of the ankle, a large proportion of patients (43.5%) also had crystals found on synovial fluid analysis.[229] Because of these findings the presence of crystals in synovial fluid should not be used to rule out bacterial arthritis, and bacterial Gram stain and culture should be performed on all joint aspirates.

Other Causes of Arthritis

RA, systemic lupus erythematous, spondyloarthropathy, Still disease, rheumatic fever, and Kawasaki syndrome typically occur with subacute polyarticular arthritis associated with specific symptoms and signs of their respective diseases. Although these conditions may be confused with viral arthritides, especially parvovirus B19 or chikungunya arthritis, they are usually easily differentiated from bacterial arthritis. More important, however, is the recognition and diagnosis of bacterial arthritis in a patient with preexisting rheumatoid or other inflammatory arthritis. A sudden increase in inflammation of one or two joints in such patients should raise suspicion of complicating bacterial arthritis, even if it is not accompanied by fever or other systemic evidence of infection, and joint aspiration should be performed.

Reactive arthritis may occur spontaneously or follow a recent gastrointestinal or genitourinary infection, particularly in men.[234] The reactive arthritis may be associated with tenosynovitis and urethritis, thus mimicking disseminated gonorrhea. Patients with reactive oligoarticular arthritis, however, do not display the characteristic rash of DGI and will often have concomitant sacroiliitis, conjunctivitis, circinate balanitis, or keratoderma blennorrhagica—all conditions absent in DGI.

Hemarthrosis caused by trauma or intraarticular injury can mimic septic arthritis of the knee. In such cases a history of injury is readily apparent. For the rare case of septic arthritis after blunt, nonpenetrating trauma, an aspiration with synovial fluid analysis, and culture is required to establish the diagnosis.

Therapy

Joint Drainage

The management of acute bacterial arthritis requires prompt joint drainage, in addition to antimicrobial therapy. One approach to drainage is through daily closed-needle aspiration of affected joints until there is clinical improvement and the amount and degree of purulence of synovial fluid is minimal. Surgical modalities for drainage include arthroscopy and open arthrotomy, both of which allow visualization and irrigation of the joint, lysis of adhesions, and removal of thick purulent material and inflammatory mediators.[235–239] The choice of drainage procedure may depend on the available clinical resources and should be adapted for the individual patient and involved joint. Needle aspiration is less invasive and may be considered if the joint is easily accessible and can be adequately drained, and if the patient lacks negative prognostic factors.[235]

For bacterial infection of the knee, hip, shoulder, wrist, and ankle, drainage by arthroscopy is usually preferred and may need to be repeated for more severe infections.[236–245] For these joints an arthroscopic approach has similar or improved outcomes compared with open surgery with fewer complications and less need for a repeat drainage procedure. Risk factors for failure of a single surgical débridement include a history of inflammatory arthropathy or diabetes mellitus; involvement of the knee, shoulder; or hip; synovial fluid cell count >85,000 cells/mm^3, and *S. aureus* as the bacterial isolate.[246] Timeliness of débridement is likely an additional important prognostic indicator. One study showed that joint washout within 24 hours of diagnosis shortened hospital length of stay compared with a >24-hour delay, but pathogen type and comorbid conditions did not.[247]

Antimicrobial Therapy

Antimicrobial therapy for native joint bacterial arthritis should be initiated without delay to limit articular destruction, preferably after synovial fluid cultures have been obtained. There are no randomized controlled trials that have evaluated antimicrobial regimens for septic arthritis; thus sound evidence is lacking to guide therapeutic options. A large meta-analysis of antimicrobial therapy for bacterial arthritis did not show an advantage of any one, or combination of, therapeutic agent(s)

over another.[248] Initial antibiotic selection is dictated by synovial fluid Gram stain or likely infecting pathogens, or both, as determined by the clinical presentation (Table 103.5; also see Tables 103.2 and 103.3). Risk factors for infection by an antimicrobial resistant pathogen should be considered.

Initial antimicrobial selection. Vancomycin is indicated as empirical therapy for persons with gram-positive cocci on a synovial fluid Gram stain or as a component of therapy for those with a negative Gram stain because of the high prevalence of health care–associated MRSA and CA-MRSA joint infection. For patients with gram-negative rods on Gram stain, an antipseudomonal cephalosporin or piperacillin-tazobactam should be used unless there is a recent or concurrent infection or colonization by an extended-spectrum β-lactamase–producing pathogen, in which case a carbapenem antibiotic is preferred. Aztreonam or ciprofloxacin are less desirable alternatives due to a relatively high proportion of antimicrobial resistance to these agents in many gram-negative pathogens. Injection or infusion of antibiotics directly into the joint is not recommended. For patients with a negative Gram stain, empirical therapy is appropriate even if they have only a modest probability of septic arthritis. In these cases vancomycin plus an antipseudomonal cephalosporin or piperacillin-tazobactam should be used.

For patients with a well-documented or described history of serious allergy to penicillin, in most instances a carbapenem antibiotic can be given. For those with a remote or poorly documented or described penicillin allergy, a cephalosporin antibiotic is often tolerated. Penicillin skin testing, followed by an oral cephalosporin challenge, is useful for determining true immunoglobulin E–mediated allergy and is increasingly available for inpatients in acute care hospitals.

TABLE 103.5 Recommended Empirical Therapy for Adult Native Joint Bacterial Arthritis

GRAM STAIN	PREFERRED ANTIBIOTIC[a]	ALTERNATIVE ANTIBIOTIC
Gram-positive cocci	Vancomycin, 15–20 mg/kg (ABW) daily every 8–12 h[b]	Daptomycin, 6–8 mg/kg daily[c] *or* linezolid, 600 mg IV or PO every 12 h[c]
Gram-negative cocci[d]	Ceftriaxone, 1 g every 24 h	Cefotaxime, 1 g every 8 h[e]
Gram-negative rods[f]	Ceftazidime, 2 g every 8 h *or* Cefepime, 2 g every 8 h *or* Piperacillin-tazobactam, 4.5 g every 6 h	Carbapenem[g,h] (preferred alternative) *or* Fluoroquinolone[i] Aztreonam, 2 g every 8 hr
Gram-stain negative[f]	Vancomycin *plus* Ceftazidime *or* Cefepime *or* Piperacillin-tazobactam	Daptomycin[c] *or* linezolid[c] *plus* Carbapenem[g,h] (preferred alternative) *or* Fluoroquinolone[i] Aztreonam

[a]Unless noted otherwise, dosages are IV for persons with normal renal function.
[b]Therapeutic monitoring should target a serum area under the concentration-time curve to minimal inhibitory concentration of 400 to 600 mg-h/L.
[c]See text discussion under "Directed Therapy for MRSA Infections."
[d]Equivocal gram-negative morphology should be considered as gram-negative rods.
[e]Gram-negative cocci with epidemiology or history suggestive of gonococcal infection should be initially treated per Centers for Disease Control and Prevention Sexually Transmitted Disease Guidelines. Alternative therapies have not been suggested for patients with a history of a Stevens-Johnson syndrome or severe IgE-mediated allergy to β-lactam antibiotics. Possible empirical options for penicillin-allergic patients, pending culture sensitivities, include azithromycin, ciprofloxacin, tobramycin, gentamicin, and spectinomycin (not available in the United States).
[f]For patients with risk factors for resistant gram-negative pathogens (significant health care exposure, immunosuppression, or recent history of extended-spectrum β-lactamase gram-negative infection or colonization), drug selection should consider regional or local antibiograms.
[g]Imipenem, 500 mg every 6 h; *or* meropenem, 1 g every 8 h.
[h]Usually reserved for patients with penicillin allergy or risk factors for resistant gram-negative pathogens (significant health care exposure, immunosuppression, or history of extended-spectrum β-lactamase gram-negative infection or colonization).
[i]Ciprofloxacin, 400 mg IV every 8 h or 750 mg PO every 12 h *or* levofloxacin, 750 mg IV or PO every 24 h.
ABW, Actual body weight; *IgE,* immunoglobulin E; *IV,* intravenous; *PO,* by mouth.

Antimicrobial deescalation. Empirical treatment should be narrowed or deescalated based on the identity and antimicrobial susceptibility of bacteria identified in synovial fluid, blood, or, in some cases, ancillary cultures or test (e.g., mucosal culture or NAAT for gonococci). For cases where MSSA is isolated, therapy should be narrowed to an antistaphylococcal penicillin (e.g., nafcillin/oxacillin) or first-generation cephalosporin (e.g., cefazolin). Although ceftriaxone is an attractive option for *S. aureus* osteoarticular infections because of once-daily dosing, tolerability, and lower cost, it should be noted that it is intrinsically less active than standard antistaphylococcal agents, and clinical evidence is limited to support its use for these infections. A small retrospective cohort study that compared ceftriaxone with oxacillin for treatment of osteomyelitis (124 patients) and septic arthritis (57 patients) did demonstrate similar treatment outcomes for both groups.[249] There were fewer patients who required discontinuation of therapy because of toxicity in the ceftriaxone group. A smaller study comparing ceftriaxone with cefazolin also found similar efficacy.[250] However, until more evidence is available, the use of ceftriaxone for *S. aureus* septic arthritis remains controversial and is not recommended.

Directed therapy for MRSA infections. For MRSA joint infections, vancomycin should be continued and therapeutic serum concentration monitoring performed to achieve an area under the concentration-time curve (AUC) to MIC ratio of 400 to 600 mg-h/L.[251]

Linezolid and daptomycin are an alternative for patients with MRSA native joint infection. In prior clinical practice most clinicians have reserved their use for patients with cultures yielding vancomycin-intermediate *S. aureus;* vancomycin-resistant enterococci; or who are allergic to, intolerant of, or not clinically responding after 3 to 5 days of vancomycin. Published experience with daptomycin in bone and native joint infection is mostly limited to case reports and open-label or retrospective, observational, and post hoc studies.[252–256] However, one nested case-control study and a single prospective, randomized, controlled trial of daptomycin in osteoarticular infections demonstrated safety and similar efficacy as comparator antibiotics.[256,257] Of note, Infectious Diseases Society of America guidelines for prosthetic joint infection suggest dosing daptomycin at 6 mg/kg/day.[258] Recent publications, however, suggest that a dose of 8 mg/kg/day may be more appropriate without increased adverse events.[259,260] In recent years daptomycin usage has increased in outpatient parenteral antimicrobial therapy (OPAT) for bone and joint infections that are confirmed or suspected to be due to gram-positive pathogens. Factors likely responsible for this increased usage include convenience factors, such as once-daily dosing, lack of requirement for serum concentration monitoring and subsequent dose adjustment, and less adverse events, compared with vancomycin.[261]

Evidence for the efficacy of the oxazolidinones, linezolid or tedizolid, in bacterial arthritis includes observational studies, mostly in prosthetic joint infections and osteomyelitis, and a trial in osteoarticular infections in children.[262–268] Because linezolid is an oral agent with excellent bioavailability, it has appeal for treatment of staphylococcal joint infections. However, significant adverse drug events, including neuropathy, anemia, thrombocytopenia, and lactic acidosis, have somewhat limited its use for the prolonged therapy that is required for these infections.

There is considerable interest in using the long-acting lipoglycopeptides, dalbavancin or oritavancin, for staphylococcal (including MRSA) osteoarticular infections, including native joint septic arthritis.[269] Although expensive, these drugs can be dosed IV once per week, and for MRSA native joint septic arthritis, dalbavancin could be dosed only twice to cover the total duration of therapy.[270] Limited clinical experience suggests therapeutic efficacy for both osteomyelitis and joint infection, but further study is necessary before it can be recommended.[271,272]

Ceftaroline, a broad-spectrum cephalosporin with MRSA activity, is potentially suitable for treatment of septic arthritis, but more data is needed before it can be endorsed.[273] Like linezolid, neutropenia is associated with prolonged therapy with ceftaroline. There is very little evidence to support the use of telavancin or newer tetracycline drugs, including tigecycline, eravacycline, or omadacycline for the treatment of septic arthritis.[274]

There have been reports that the performance of vancomycin diminishes for severe infections caused by MRSA that have an isolate MIC ≥1 mg/L.[252,275,276] Further clinical studies are needed to establish

whether vancomycin in combination with rifampin or alternative drugs should be used for native joint infections caused by these organisms.

Directed therapy for other situations. For patients with a high pretest probability of septic arthritis and negative cultures who are responding to empirical therapy, the initially chosen antimicrobials should be continued to complete a full treatment course. Infections caused by animal or human bites should be treated with antimicrobials that have activity against aerobic and anaerobic oral flora, for example, ampicillin-sulbactam or amoxicillin-clavulanate, and in the penicillin-allergic patient, clindamycin plus ciprofloxacin or moxifloxacin. Gonococcal arthritis is treated initially with ceftriaxone, 1g IM or IV once every 24 hours or, alternatively, with cefotaxime or ceftizoxime, 1 g IV every 8 hours, in addition to azithromycin 1 g orally in a single dose. After improvement, oral "step-down" therapy may be substituted. The emergence of resistance to fluoroquinolones, and more recently to cefixime, limit the use of these agents for oral therapy unless culture isolates are available and sensitivity is demonstrated.[277]

Duration of therapy. The duration of therapy for septic arthritis has not been studied in controlled trials. Although therapy should be long enough to eradicate all foci of infection and thus prevent recurrence and further joint disability, the duration does not have to be as long as what is usually given for osteomyelitis. Potential variables that likely influence the duration of therapy include the particular joint involved, identity of the infecting pathogen, and host comorbidity and immune function. Traditionally, parenteral therapy for 2 to 4 weeks is prescribed, although if fluoroquinolones or linezolid (or tedizolid) are used, IV therapy can be converted to oral therapy early in the treatment course. Infections caused by *S. aureus*, including MRSA, and gram-negative bacilli generally require 4 weeks of treatment. Besides linezolid (or tedizolid), choices for oral MRSA step-down therapy after 2 to 3 weeks of parenteral therapy include trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline or minocycline, or clindamycin, depending on susceptibility. Disseminated gonorrhea or gonococcal arthritis requires 1 week of treatment.

Perhaps shorter courses of parenteral antibiotics would still be effective in selected patients. A retrospective study of adult patients showed that rates of recurrent infection and sequelae of infectious arthritis did not differ among patients who received 7 days of parenteral antibiotics, 8 to 21 days, or greater than 21 days, as long as successful drainage was performed.[278] In the same study patients who had 14 days or less of total antibiotic treatment, which included initial parenteral therapy followed by oral therapy, had no difference in recurrence rates or sequelae compared with those that received longer treatment courses. Risk factors for recurrence of infection in the study included immune suppression and the lack of surgical intervention. A second retrospective study of 14 days of antimicrobial therapy for pyogenic arthritis of the fingers and wrist reported good outcomes if surgical débridement was adequate.[279] Although it is difficult to recommend a duration of antibiotic therapy based on these findings, it is reasonable to assume that a shorter duration of therapy in an immunocompetent patient who has undergone an adequate drainage procedure might be appropriate. Clinical trials to conclusively answer the question of optimal duration of therapy are needed.

Adjuvant Therapy

Current research is examining whether adjuvant therapy directed at the attenuation of microbial virulence factors or the host inflammatory response is able to reduce the sequelae of bacterial joint infection.[24,50] There is growing evidence that adjuvant early, short-course, systemic corticosteroid treatment for children with hematogenous bacterial arthritis significantly reduces the duration of symptoms, hospitalization, antibiotic therapy, and residual joint dysfunction.[280–283] Widespread application of these findings to clinical practice is pending upcoming guideline recommendations and studies in other populations of patients. Animal studies have examined TNF-α antagonists, IL-12, recombinant IL-10, and bisphosphonates as adjuvant treatments with some benefits.[24,148] Although these approaches look promising, further research is needed.

VIRAL ARTHRITIS

Arthritis or arthropathy caused by viral agents is often acute, occurs concurrently with signs and symptoms of febrile systemic illness, and resolves along with other manifestations of illness. Viruses may cause arthritis directly by infecting the synovium or indirectly through host immune-mediated responses, and much of the pathogenesis is poorly understood.[284,285]

Parvovirus B19

Perhaps the most common form of viral arthritis in developed countries is caused by human parvovirus B19. In children human parvovirus B19 infection arises with fever, rash, coryza, headache, and malaise.[286] The rash classically arises with bright red "slapped checks" and a lacy, reticular exanthem on the torso and extremities. Arthritis occurs in less than 5% of afflicted children and tends to be asymmetrical and pauciarticular, and it predominantly affects the knee.[287,288]

Adults who become infected with human parvovirus B19 do not display the classic facial erythema noted in children and present with a febrile, flulike illness with prominent polyarthralgia and joint inflammation accompanied by an absence of reticulocytosis.[284,287,289] Cases are usually seen in late winter and early spring, and regional and nosocomial outbreaks of disease have been reported.[290–293] An associated exanthem, if apparent, is a fleeting and difficult-to-appreciate rash on the torso and, less often, on the extremities, which may show some of the reticular aspects exhibited by children (Fig. 103.5). Arthritis or prominent arthralgias are more common in females than men with human parvovirus B19 infection, affecting 60% and 30% of individuals, respectively.[287,294] Characteristically, an acute and moderately severe, symmetrical polyarthritis of the proximal interphalangeal and metacarpophalangeal joints is associated with morning stiffness and somewhat resembles RA.[286,287,295] Knees, wrists, and ankles may also be involved. In approximately one-third of patients, particularly women, joint symptoms occur in episodic flares with symptom-free intervals.[286] A biphasic illness may manifest in some patients with an acute febrile illness that is separated from rash and joint symptoms by several days.[296] Diagnosis is made clinically, and a positive serologic or peripheral blood PCR test supports the diagnosis, although false-positive and -negative results occur with both tests.[284,285,297]

Although joint symptoms usually resolve within 2 weeks, persistent polyarticular arthritis may follow acute human parvovirus B19 infection in up to 20% of female patients and, in some individuals, may last up to several months, occasionally longer.[284,286,298] In such patients joint erosions and objective evidence of synovial inflammation do not develop,[286] and follow-up studies do not demonstrate long-term joint swelling or restricted range of motion consistent with true chronic arthritis.[299] Treatment of chronic human parvovirus B19 arthritis is supportive with nonsteroidal antiinflammatory drugs (NSAIDs), and, except in exceptional cases, IV immunoglobulin is not indicated.[284,300] The role of human parvovirus B19 in the pathogenesis of RA or systemic lupus erythematosus remains circumstantial and inconclusive.[285,287,301]

FIG. 103.5 **Faint, lacy reticular rash of the proximal lower extremities characteristic of adult human parvovirus B19 infection.**

Alphaviruses, Including Chikungunya

Several alphavirus infections are associated with arthritis and are distributed worldwide, particularly in tropical and subtropical regions.[285,302,303] These arboviruses usually cause sporadic and endemic disease; however, viral mutation or an increased prevalence of their mosquito vectors may result in periodic explosive outbreaks of fever, rash, and arthritis.[284,303,304] In 2005 an outbreak of chikungunya virus infection emerged in the islands of the Indian Ocean, afflicting more than 300,000 persons over a 2-year period before extending to South and Southeast Asia, followed by Oceania, where it was responsible for millions of additional suspected cases.[303–306] Subsequently the virus quickly spread into the New World, and cases were reported in the Caribbean in 2013, followed by South America the following year.[303] The ensuing outbreak in the Western Hemisphere peaked in early 2016 with millions of additional cases occurring over the prior 2-year period. These included several imported and a handful of locally acquired cases in the continental United States.[307] Since 2016 the virus has remained endemic throughout the tropics and subtropics worldwide.

Chikungunya virus is transmitted by the bite of the daytime-biting *Aedes* spp. mosquitoes. The presence of the mosquito vector, *Aedes albopictus*, in Europe and the Americas, together with returning travelers with extremely high levels of viremia, is a public health concern in that infection could be easily established in these previously nonendemic subtropical regions.[304,306,308,309]

Chikungunya fever is characterized by an acute biphasic febrile illness, with the initial phase manifesting headache, malaise, myalgias, symmetrical arthralgias, or polyarthritis, and in approximately 50% of cases, a skin rash (Fig. 103.6).[302–305,308,309] Joint symptoms are often quite severe (chikungunya means "that which contorts or bends up"), affecting predominantly the wrist, ankles, and small joints of the hands and feet. After 5 to 7 days of fever and a brief interlude of improved symptoms, a polyarthritis with or without tenosynovitis often recurs and may be disabling.[303,304,308,310] Some cases may resemble dengue fever or Zika virus infection, both of which are also highly endemic in regions where chikungunya fever occurs. Similar to infection caused by human parvovirus B19, a chronic form of chikungunya virus–associated arthritis has also been described.[311,312] A meta-analysis including 6532 patients with chikungunya virus arthritis showed that 43% did not fully recover after 3 months, and 21% were still symptomatic within 1 year. In many patients symptoms persisted for more than 28 months.[311] Up to one-fourth of those afflicted rated their symptoms as severe. Older age, female gender, and symmetrical joint involvement during the acute phase were associated with persistence of joint symptoms. In addition, the level of acute chikungunya viremia may also be a factor.[313] A different experience has been reported from a rheumatology clinic in the Dominican Republic, where the mean duration of symptoms was 2.5 months, and 89% of 457 patients presenting with chikungunya virus infection responded well to NSAIDs, although 72% were treated with low-dose glucocorticoids (e.g., 5–7.5 mg of prednisone daily). RA patients, all of whom had been on DMARDs, including biologic agents such as TNF-α antagonists, rituximab, or tocilizumab, did equally well.[314]

FIG. 103.6 Erythematous maculopapular rash with islands of normal skin characteristic of chikungunya virus infection. *(From Hochedez P, Jaureguiberry S, Debruyne M, et al. Chikungunya infection in travelers.* Emerg Infect Dis. *2006;12:1565–1567.)*

Diagnosis of chikungunya fever–associated arthritis is based on clinical, epidemiologic, and laboratory criteria. Tests of acute and convalescent serum with PCR and indirect immunofluorescence and enzyme-linked immunosorbent assay serology are most useful.[303–305,308,309] Other arboviruses that cause alphaviral arthritis include o'nyong-nyong, igbo-ora, Ross River, Barmah Forest, Sindbis, and Mayaro viruses.[302]

Other Causes of Viral Arthritis

Rubella is another important cause of viral arthritis in adults, particularly in the developing world, where childhood vaccination is not widespread. Joint inflammation may follow natural infection or immunization with live-attenuated vaccine.[284,315] Arthritis is thought to occur via direct infection of joint synovial tissue, although immune complexes may also play a role.[285,316,317] As with human parvovirus B19, the polyarthritis that is associated with rubella affects predominantly women and most frequently involves the small joints of the hands and, less commonly, the knees, wrists, and ankles.[285,318] Joint symptoms occur simultaneously or within a few days of the rash in 52% of adult female subjects with infection by wild-type virus and within 2 to 3 weeks in 14% of adults receiving rubella vaccine.[285,318] A placebo-controlled, randomized trial showed that 30% of seronegative, adult women receiving rubella vaccine developed acute arthropathy after vaccination, as opposed to 20% of those receiving placebo, a significant difference.[319] Arthritis after rubella vaccination or natural infection may persist for several weeks, but chronic or recurring arthritis is unusual.[315,317,320] Treatment is supportive, with NSAIDs or low-to-moderate doses of corticosteroids.[284]

In acute hepatitis B infections severe arthralgia or arthritis may be seen during the febrile prodrome before the onset of jaundice and is often seen together with urticaria.[284,321,322] A symmetrical, polyarticular arthritis typically involves the hands, wrists, knees, or ankles and resolves with the onset of jaundice. The clinical findings may resemble a RA syndrome in the acute infection period, and a positive rheumatoid factor may be seen in 40% of patients.[321] Although an association between chronic hepatitis B and RA has been hypothesized, sound evidence for this is lacking.[321,323]

Arthritis in the setting of hepatitis C virus (HCV) infection is poorly described.[284,321] Joint symptoms are noted in up to 50% of HCV-infected patients, although only 2% to 4% have frank arthritis.[284,321] It is controversial whether HCV infection is associated with a distinct inflammatory arthritis syndrome, although there is growing evidence that a rare nonerosive inflammatory arthritis mimicking RA may occur.[284,321] In chronic hepatitis B– or hepatitis C–induced essential mixed cryoglobulinemia, arthralgias, and fibromyalgia are described as occurring in approximately one-third of patients, although frank arthritis is not usually observed.[321,324,325]

Both HIV-1 and human T-cell leukemia virus 1 (HTLV-1) are retroviruses with the ability to cause arthritis or arthropathy.[284,326] Nonspecific joint pain is common in the setting of HIV infection, although true articular manifestations of HIV-1 are rare and include chronic arthralgia and oligoarticular arthritis.[284,327,328] An increased incidence of reactive and psoriatic arthritis has been observed in patients with HIV, particularly among MSM.[284,327] Some elderly patients in Japan infected with HTLV-1 have been described with a chronic joint infection termed HTLV-1–associated arthropathy, which closely resembles RA (see Chapter 168).[326,329]

Musculoskeletal complaints in survivors of Ebola virus infection is common, with 70% complaining of myalgia and arthralgia 3 weeks after hospital discharge.[330,331] Longer-term joint complications in these patients may include symmetrical polyarticular arthralgia and arthritis, enthesitis, and tendon rupture. Overt joint inflammation is usually not apparent.

CHRONIC INFECTIOUS ARTHRITIS

Chronic infectious arthritis consists of a constellation of monoarticular or, less commonly, oligoarticular joint infections that are characterized

TABLE 103.6 Infectious Causes of Chronic Monoarticular or Oligoarticular Arthritis

Bacterial
Borrelia burgdorferi
Tropheryma whipplei
Treponema pallidum
Nocardia spp.
Fungi
Candida spp.
Cryptococcus neoformans
Blastomyces dermatitidis
Coccidioides spp.
Paracoccidioides brasiliensis
Sporothrix schenckii
Aspergillus spp. and other molds, including *Rhizopus, Scedosporium,* and *Fusarium*
Mycobacteria
Mycobacterium tuberculosis
M. kansasii
M. marinum
M. avium-intracellulare complex
M. terrae
M. fortuitum, M. chelonae, M. abscessus
M. haemophilum
M. leprae
Parasites
Helminths
Filariae

by an insidious onset and indolent course, a paucity of symptoms, and progressive joint destruction that may result in considerable loss of articular function. Many of these infections arise with few symptoms and signs of joint inflammation other than subacute or chronic joint swelling, with or without effusion, and pain and stiffness during active range of motion. Although this form of infectious arthritis remains relatively uncommon compared with the incidence of acute septic arthritis, it is a significant component of the differential diagnosis of subacute or chronic joint inflammation. An increasing number of anecdotal reports indicate that it is an emerging problem in immunocompromised or chronically ill hosts. Noteworthy aspects of this entity include its ability to mimic other inflammatory joint disorders, such as RA, and its ability to arouse little clinical suspicion, resulting in considerable delays in diagnosis. Moreover, establishing a pathogen-specific diagnosis is difficult, and the response to treatment is slow and often incomplete. Inappropriate treatment—for example, systemic or intraarticular steroids for a tentative diagnosis of RA—is not uncommon and can further delay diagnosis and/or lead to more rapid or severe joint destruction. Subacute or chronic infectious arthritis is usually caused by mycobacteria or fungi, and occasionally by bacteria, such as *B. burgdorferi, T. whipplei, Treponema pallidum* (tertiary syphilis),[332] and *Nocardia* (Table 103.6).[333] Chronic arthritis caused by parasitic infection is rarely described with various helminths and filiariae, despite the large number of persons infected with these parasites each year.[334]

Fungal Arthritis

Fungal arthritis may sometimes occur in normal hosts; however, in immunocompromised or chronically ill persons, a steadily increasing frequency of infection and diversity of infecting mycotic pathogens is apparent.[335,336] Although there is some overlap between the two groups, the most common fungal pathogens isolated from infectious arthritis in healthy hosts residing in endemic regions for the dimorphic fungi are *Blastomyces dermatitidis, Coccidioides* spp., and *Sporothrix* spp., whereas in immunocompromised hosts, *Candida* spp., *Cryptococcus,* and *Aspergillus* or other molds are more often observed.[335–337] However, pulmonary and disseminated infections caused by the dimorphic fungi are increasingly diagnosed in patients with RA or IBD on TNF-α inhibitor therapy, and these drugs are likely a risk factor for chronic fungal arthritis.[338,339] Joint infection from fungal pathogens usually results from hematogenous dissemination of the organism and, except for *Candida,* has as its source a symptomatic or subclinical respiratory tract infection. On occasion, a fungus, usually a mold, is introduced into the joint via direct trauma or injury, sometimes associated with a penetrating foreign body.[336,340,341]

Candida Arthritis

Candida arthritis afflicts both native and prosthetic joints and has been increasing in frequency over the last 2 decades, parallel to the rising incidence of systemic and focal infections caused by this organism in hospitalized and chronically ill patients.[342–344] Risk factors for joint infection with this organism include loss of skin integrity, diabetes mellitus, hemodialysis, malignancy, malnutrition, premature birth, IVDU, immunosuppressive therapy (including corticosteroids), and the prolonged use of broad-spectrum antimicrobials, hyperalimentation fluid, and central IV catheters.[335,343–345] In most cases articular infection occurs through the hematogenous route, with normal joints typically afflicted in a monoarticular pattern, although polyarticular infection occurs in up to 30% of cases.[344] Infection can also occur by direct inoculation of the joint through surgery or corticosteroid injection, particularly in arthritic or surgically altered joints.[335,344,346] Patients are often heavily colonized by *Candida* at skin, gastrointestinal, or mucosal sites before joint infection. *Candida albicans* is the most commonly isolated species,[343,344] followed by *C. tropicalis*, and *C. parapsilosis*. Other less commonly cultured species include *C. glabrata, C. krusei, C. guilliermondii, C. zeylanoides, C. lambica, and C. lusitaniae.*[335,343,346–351] As in bacterial arthritis, the knee is affected in the vast majority of cases and less often the hip or other joints.[343,344] In IV drug abusers fibrocartilaginous joints, including the sternoclavicular, sacroiliac, and costochondral, may be involved. In addition, they may manifest with associated *Candida* endophthalmitis, and folliculitis of the face, scalp, and torso.[352] *Candida* arthritis may arise acutely, with complaints of marked joint inflammation and associated fever and constitutional symptoms, especially in cases accompanied by systemic candidiasis or, more insidiously, with chronic indolent joint pain and stiffness and minimal systemic manifestations.[344,346] In the latter case a long latent period is often seen between an episode of apparent or suspected occult candidemia and the onset of joint complaints. Extension of infection from the joint to adjacent bone is not uncommon.[335] Synovial fluid analysis characteristically shows polymorphonuclear leukocytosis with cell counts greater than 25,000 cells/mm^3 and a normal or low measured glucose. Gram stain of synovial fluid is not usually diagnostic, although bacterial or fungal culture yields *Candida* spp. in most cases. Blood cultures are positive in less than 30% to 50% of patients.

Cryptococcus Arthritis

Cryptococcus neoformans causes skeletal infections in less than 10% of patients with disseminated infection with this organism.[353–355] Cryptococcal arthritis is considerably less common than cryptococcal osteomyelitis, and the latter is frequently the nidus of infection for the former through local contiguous spread. The majority of patients with joint infection caused by this organism are immunocompromised because of various conditions, including acquired immunodeficiency syndrome.[355,356] The presentation of cryptococcal arthritis and associated osteomyelitis is that of a chronic joint infection, most often involving the knee.[335,355] A serum cryptococcal antigen test is often positive.[354] Diagnosis requires joint aspiration or synovial biopsy with appropriate synovial fluid or tissue fungal cultures. Of importance, with rare exceptions, osteoarticular infection represents disseminated cryptococcal disease; thus coexisting infection of the central nervous system should be ruled out.

Arthritis Due to Dimorphic Fungi

Acute infection caused by *Coccidioides immitis* or *Coccidioides posadasii* occurs in the southwestern region of the United States, northern Mexico, and a few regions of Central and South America, causing a symptomatic or subclinical primary pneumonitis. Migratory polyarthralgia and polyarticular arthritis occur in approximately one-third of these patients, manifesting as a self-limited hypersensitivity syndrome termed "desert rheumatism" or "valley-fever."[336] In about 1% of persons with coccidioidomycosis, dissemination occurs, and although any host may be afflicted, it is more likely in men, pregnant females, Blacks, Filipinos,

and immunocompromised persons, including patients with HIV infection.[357,358] Skeletal involvement occurs in approximately 30% of such cases and results in a chronic granulomatous infection of bones, joints, and periarticular tissues.[335,337,357] Joint infection may be primary or secondary to extension from contiguous osteomyelitis. Weight-bearing joints, particularly the knees and ankles, are most frequently affected, but any joint may be involved.[337,357,359] Presentation is that of subacute or chronic monoarticular or polyarticular arthritis that may progress either slowly or quite rapidly, resulting in extensive joint destruction.[357,360,361] Other manifestations of disseminated infection are not uncommon at the initial evaluation.[357] Peripheral eosinophilia may be present, and synovial fluid leukocyte counts are moderately elevated, with a lymphocytic predominance. Coccidioidal arthritis should be considered in patients presenting with chronic progressive arthritis in endemic areas. Diagnosis is suggested by an elevated titer against coccidioidal antigens on serologic testing of serum, or visualization of spherules in synovial fluid. Confirmation is by fungal culture of synovial fluid and histopathologic examination and culture of synovial or periarticular tissues.[362] In suspected cases of coccidioidal arthritis the microbiology laboratory should be alerted before sending specimens for culture because *Coccidioides* spp. are important biohazards in the clinical laboratory. Once isolated, shipping the isolate for confirmation of identity is complicated because the organism is a potential agent of bioterrorism, and its transport is strictly regulated.[363]

Similar to coccidioidomycosis, blastomycosis is primarily a pulmonary infection that may later disseminate, potentially involving the bones and joints. Skeletal infection caused by *Blastomyces dermatitidis* occurs in about one-fourth of patients with disseminated infection, and joint infection in most cases is associated with juxtaarticular osteomyelitis.[364] Monoarticular arthritis of the knee is most common, followed by the ankle, elbow, wrist, and hand.[335] Polyarticular infection is extremely rare.[365,366] An acute arthritis with abrupt onset and accompanying systemic symptoms of inflammation and a more chronic joint infection are both described.[365,367] Concomitant blastomycosis pneumonia and nodular or ulcerative skin lesions are frequently evident on examination, and periarticular draining sinus tracts are occasionally seen.[336] Synovial fluid is purulent, and organisms are readily demonstrated on cytologic examination or microscopic examination of a wet mount smear.[368] Cultures of synovial fluid or other affected locations will usually confirm the diagnosis.

Histoplasma capsulatum is an extremely rare cause of fungal arthritis in endemic areas and is usually associated with immunosuppression. A chronic monoarticular arthritis of native and prosthetic knee joints has been described.[369,370] In addition, a hypersensitivity syndrome with rash and arthralgia may accompany *Histoplasma* primary infection, which is similar to that in coccidioidomycosis.[371,372]

Sporotrichosis is a chronic infection caused by *Sporothrix* spp. that primarily affects the skin and secondarily the lymphatics after percutaneous inoculation by a contaminated foreign body that comprises plant or soil material (see Chapter 259 for new *Sporothrix* spp. names). In contrast to the other endemic mycoses, primary pulmonary infection is uncommon. Osteoarticular sporotrichosis comprises approximately 80% of extracutaneous infections and results from hematogenous dissemination rather than from direct joint inoculation. On occasion, hematogenous spread to the skin occurs at the same time. The portal of entry is usually not apparent, although a pulmonary portal is sometimes evident. At most, only 0.3% of patients with cutaneous sporotrichosis will develop arthritis.[335,373] Immunocompromised, diabetic, and alcoholic patients are at higher risk for disseminated infection and arthritis,[374–376] and the typical patient is a male involved in gardening, farming, or an outdoor occupation.[377,378] Chronic monoarticular or polyarticular sporotrichosis arthritis arises in the knees, wrists, hands, elbow, and ankle, and a tenosynovitis has also been reported.[335,378,379] Symptoms and signs are more prominent in the small joints of the wrist and ankle. Fever is uncommon, and there are usually no other focal symptoms or signs of infection, including pulmonary or cutaneous, before or during the course of arthritis.[376,378] Diagnosis is difficult because organisms are rarely found on histologic examination of joint fluid or tissue, and fungal culture of these specimens is often negative. Multiple aspirations and biopsy of affected joints may be necessary. As a result, extremely long diagnostic delays and permanent joint sequelae are common.[380]

Arthritis Due to Molds

Molds, including *Aspergillus,* are an exceedingly rare cause of septic arthritis, with the majority of cases having been reported in association with disseminated infection in immunocompromised hosts or introduction by trauma.[381,381a] One review described 31 cases of *Aspergillus* septic arthritis and noted the knee and hips to be the most frequently infected joints.[381a] Many patients had oligoarticular involvement due to hematogenous seeding. *Aspergillus fumigatus* constituted 77% of cases, followed by *A. flavus* in 13% and *A. niger* in 3%. Osteolysis and tissue extension were common. Synovial fluid WBC count varied considerably, with a median of 17,200 cells/mm^3. Prognosis was poor, with an overall survival of 65%.

Fungal arthritis caused by *Fusarium* spp., *Curvularia* spp., *Exophiala* spp., *Trichosporon asahii, Lomentospora (Scedosporium) prolificans, Scedosporium apiospermum* (*Pseudallescheria boydii*), and Mucorales have all been described and may be seen in either immunocompromised or immunocompetent patients.[382–387] A review of 43 years of reports of non-*Aspergillus* mold osteoarticular infections found antecedent trauma in children and prior surgery in adults as risk factors.[388] Hyaline molds were the most common agents reported, among which *S. apiospermum* and *L. prolificans* were most frequent. All of these pathogens usually cause severe joint infections that respond poorly to antifungal therapy.

Bone and joint infection caused by *Aspergillus* spp. and *Rhizopus* spp. have complicated arthroscopic anterior cruciate ligament reconstruction in young healthy persons.[389,390] Mold infections after intraarticular steroid injections in immunocompetent hosts have also been reported.[381,391] In the fall of 2012 a multistate outbreak of fungal infection associated with the injection of contaminated methylprednisolone acetate from a single compounding pharmacy resulted in several cases of fungal meningitis, vertebral osteomyelitis, epidural abscess, and peripheral joint infection. Altogether, there were 33 cases of peripheral joint infection caused by *Exserohilum* spp., some of which presented several months after joint injection with contaminated steroid.[34,143,392]

Therapy for Fungal Arthritis

A combined approach to therapy for fungal native joint arthritis, using medical and surgical modalities, is typically necessary for optimal results. Open or arthroscopic débridement and drainage should be performed, at which time tissue and fluid specimens can be obtained for histopathologic and microbiologic testing. However, when a diagnosis of cryptococcal, or perhaps *Sporothrix* or coccidioidal, joint infection has already been established, drainage and débridement are often not necessary.[393,394]

Historically, most of the clinical experience with therapy for fungal arthritis was with amphotericin B, with or without the addition of flucytosine. In the past 2 decades fluconazole, newer extended-spectrum triazoles (itraconazole, voriconazole, posaconazole, and isavaconazole), terbinafine, and the echinocandin-class antifungals (caspofungin, micafungin, and anidulafungin) have expanded the therapeutic options available for many fungal pathogens.[395–400] In addition, lipid preparations of amphotericin B have modestly reduced the toxicity of this drug, increasing the safety of long-term amphotericin therapy.

Treatment guidelines for native joint *Candida* arthritis are based on case reports and open-label series. Antifungal susceptibility testing should be performed on all culture isolates. Recommendations include fluconazole, 400 mg (6 mg/kg) daily for at least 6 weeks or an IV echinocandin daily for at least 2 weeks, followed by fluconazole to complete therapy.[401] Alternatively, a lipid formulation of amphotericin B, 3 to 5 mg/kg/day, can be used in place of the echinocandin, although the risk of nephrotoxicity makes this choice less appealing. Courses of therapy longer than 6 weeks are frequently necessary. Fluconazole, if used, may be given orally. Echinocandins are the preferred therapy for *C. glabrata* and *C. krusei* joint infections. Oral voriconazole can be considered for step-down therapy for septic arthritis due to *C. krusei,* as most isolates are susceptible to this drug.[401–403] The incidence of *Candida* resistance to echinocandins is quite low, whereas the proportion demonstrating azole resistance depends on the species.[402,404] Surgical

débridement, sometimes multiple procedures, is indicated in all cases of *Candida* arthritis.[401] Successful eradication of *Candida* joint infection is best confirmed by posttreatment synovial fluid analysis and culture.

For cryptococcal arthritis the choice of treatment depends on the extent of disseminated disease and the immune status of the patient. In general, initial therapy with an amphotericin B preparation plus/minus flucytosine, followed by oral fluconazole, is appropriate, but in nonimmunocompromised patients with isolated septic arthritis, treatment with fluconazole, 400 mg daily for 6 to 12 months, may be appropriate.[393]

The preferred treatment of isolated joint infection without central nervous system involvement caused by the endemic mycoses, including *Coccidioides, Blastomyces, Histoplasma,* and *Sporothrix*, is with itraconazole, 200 mg twice daily for at least 12 months, unless the patient has limb-threatening skeletal disease, in which case an induction course of an amphotericin B preparation is advised.[394,405–407] Measurement of serum itraconazole levels is suggested during therapy. Coccidioidal joint infection can also be treated with high doses of fluconazole (400–800 mg daily). With either drug, a longer duration of therapy may be necessary.[406] Available evidence suggests that, for these pathogens, therapy of arthritis with itraconazole is equivalent to that with amphotericin B. The role of voriconazole, posaconazole, and isavuconazole is unclear in the treatment of the endemic mycoses.

For bone and joint infection caused by *Aspergillus,* aggressive surgical intervention is recommended. Voriconazole does appear to be effective for therapy, and most experts recommend it preferentially to amphotericin B preparations.[381,408] Other agents with activity include posaconazole, isavuconazole, and itraconazole, but there is little experience using these agents for *Aspergillus* arthritis. Unfortunately, although still unusual in the United States, intrinsic and acquired resistance to voriconazole and other azole antifungals may be emerging in *Aspergillus* spp.[409] Treatment recommendations from the CDC for empirical coverage of contaminated steroid injection–related *Exserohilum* spp. osteoarticular fungal infections that do not involve the spine are for voriconazole alone for less severe infections and a lipid formulation of amphotericin B, in addition to voriconazole, for more severe infections.[410] The use of combination therapy with voriconazole and caspofungin in fungal arthritis caused by *Aspergillus* has been described, but the role of this remains unclear.[381]

Mycobacterial Arthritis

Tuberculosis Arthritis

Worldwide, approximately 10% to 11% of extrapulmonary tuberculosis (TB) involves the bone and joints, accounting for 1% to 3% of all TB cases.[411] The incidence is higher in the developing world and is increasing because of the escalating prevalence of HIV disease. In endemic regions of the developing world, TB arthritis is mostly a disease of children and young adults, whereas in other regions, older adults and immunocompromised hosts are predominantly afflicted. Risk factors for TB arthritis include age older than 65 years, female sex, immigration from regions with high TB endemicity, a lower socioeconomic class, incarceration, alcohol abuse, debilitating illness, IVDU, immunosuppressive drug therapy (including corticosteroids and TNF inhibitors), HIV infection, and preexisting joint disease.[411–416] Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculous arthritis have been reported.[417–419]

Clinical Features

Mycobacterium tuberculosis causes a chronic granulomatous monoarticular arthritis that is usually a result of the hematogenous dissemination associated with primary pulmonary TB.[413,415] Articular infection may remain latent for long periods before clinical presentation. It typically involves the knee, hip, and ankle but can involve any joint.[413,416,417,420] The clinical presentation is that of chronic arthritis, indistinguishable from that with other potential infectious or noninfectious causes (Fig. 103.7). Long-standing cases may develop an articular-cutaneous fistula, whereas TB arthritis of the wrist may involve the periarticular tendon sheaths arising with a carpal tunnel syndrome.[420,421] Coexisting pulmonary or other extraarticular infection may be evident, but in more than half of cases it is not.[416,417,420] Fever and other constitutional symptoms of TB are often absent. Interferon-γ release assay or tuberculin skin testing is positive in 85% to 90% of patients.[413,416,422]

FIG. 103.7 Chronic arthritis of the knee resulting from *Mycobacterium tuberculosis,* exhibiting joint swelling, effusion, and a draining sinus fistula.

Diagnosis

To prevent unacceptable delays in diagnosis and further joint destruction, a high index of suspicion for TB arthritis must be maintained, particularly for patients who are immigrants from regions with high TB endemicity and those with other risk factors for TB. In the absence of known extraarticular TB, diagnosis requires synovial fluid analysis and, in many cases, synovial biopsy. Synovial fluid demonstrates inflammatory changes, with leukocyte counts characteristically between 10,000 cells/mm^3 and 20,000 cells/mm^3, although higher counts in the range seen with bacterial arthritis may be present.[420] Staining of synovial fluid demonstrates acid-fast bacilli in a minority of joint aspirates; however, mycobacterial culture yields *M. tuberculosis* 80% of the time. The most sensitive means of confirming the diagnosis has traditionally been synovial biopsy, in which the characteristic histopathology of caseating or noncaseating granulomas can be correlated with tissue mycobacterial staining and culture, the latter being positive in about 90% of specimens.[420] Mycobacterial susceptibility tests should be performed on all culture isolates.

The use of PCR assay of synovial fluid for the diagnosis of tuberculous arthritis has shown promise and can provide a rapid and minimally invasive diagnosis.[423–425] Sensitivity and specificity in one study was 82% and 91%, respectively, with a positive and negative predictive value of 90% and 84%, respectively. The same study found that of 98 patients with joint TB, 82.7% were positive for TB by PCR assay, 6.1% were positive by acid-fast staining, and 17.3% were positive by culture. These findings highlight the poor performance of traditional techniques when compared with PCR assaying.[423] The limitations of PCR assaying include false-positive tests caused by laboratory contamination and nonavailability in some centers, particularly the developing world. Updated guidelines suggest the off-label use of FDA-cleared NAATs for TB, including PCR, on specimens collected from sites of suspected extrapulmonary TB, including synovial fluid.[426] A positive NAAT result on synovial fluid confirms the diagnosis, but a negative result may not be used to exclude TB.

Imaging findings of TB synovitis consist initially of soft tissue swelling, but later in the disease process, synovial thickening and bone destruction may be seen. The use of MRI may help differentiate tuberculous arthritis from chronic noninfectious forms of joint inflammation, including RA.[427]

Treatment

Current recommendations from the CDC for the treatment of osteoarticular TB in adults without pulmonary TB are identical to that of extrapulmonary TB (including patients with HIV or other immunosuppressive states): isoniazid (INH), rifampin (RIF), ethambutol, and pyrazinamide for 8 weeks (ethambutol may be discontinued in isolates known to be without drug resistance), followed by INH and RIF to complete 6 months of therapy (see Chapter 249).[428] Directly observed therapy is advisable for most patients, and adjuvant corticosteroids are

generally not recommended.[413] If treated early, residual joint disease is uncommon and negligible. Data is scarce regarding treatment of osteoarticular MDR TB. Treatment of MDR and XDR TB relies on susceptibility testing and is changing sufficiently rapidly that guidelines are useful but rapidly become out of date (see Chapter 249).[419] Adjuvant surgical therapy is required only for reconstruction of unstable joints or osseous structures or drainage of periarticular abscesses. Surgical therapy may also be considered in cases where optimal therapy is not possible because of toxicity or resistance.

Nontuberculous Mycobacterial Arthritis

Nontuberculous mycobacterial arthritis, unlike that caused by *M. tuberculosis*, is usually caused by direct percutaneous inoculation of these opportunistic mycobacteria into the skin, joint, or periarticular structures. Soil and water, and rarely air, are the usual sources of these uncommon joint infections. *Mycobacterium avium-intracellulare, M. kansasii, M. marinum, M. xenopi,* and *M. terrae* are the most common causes, although virtually any atypical mycobacteria may be involved.[430–433] Skeletal and joint infection caused by the so-called rapid growers (*M. chelonae, M. fortuitum, and M. abscessus)* may follow trauma or surgery.[431,434–437] These opportunistic pathogens are usually associated with water, including tap water, and thus may invade through large or small breaks in the skin. On occasion, atypical mycobacterial joint infection is acquired through the hematogenous route, usually in immunocompromised hosts, and has been reported with *M. avium-intracellulare, M. haemophilum, M. kansasii, M. fortuitum, M. abscessus,* and *M. chelonae* (see Chapter 252).[438–441]

Chronic monoarticular arthritis and tenosynovitis caused by nontuberculous mycobacteria are well described.[430,431,442,443] *M. marinum* arthritis most often affects the small joints of the hand or wrist and their overlying tendon sheaths.[432,444] Infection is acquired through preexisting or concomitant skin trauma, often minor, during contact with fresh, brackish, or salt water, or with marine animals, such as fish and crustaceans. Diagnosis of atypical mycobacterial joint or tendon infections usually requires biopsy of infected structures for histopathologic examination and culture. If *M. marinum* is suspected, cultures should be incubated at 30°C in addition to 37°C, to facilitate growth of this organism.[442] Treatment varies depending on the identity of the isolated mycobacteria. Susceptibility testing can be performed in reference laboratories and is useful in directing therapy for some of these organisms.

Mycobacterium leprae has also rarely been associated with an inflammatory arthritis that often presents in conjunction with erythema nodosa leprosum (type 2 lepra reaction) (see Chapter 250).[334] This systemic reaction is caused by circulating immune complexes and, in its most severe form, presents with diffuse soft tissue, eye, ear, and nerve swelling with acute polyarthritis, particularly of the hands, wrists, and ankles. In addition, advanced Hansen disease may also be associated with chronic neuropathic (Charcot) arthritis of the peripheral joints.

SEPTIC BURSITIS

Septic bursitis is common, usually affecting the subcutaneous olecranon, prepatellar, or infrapatellar bursae.[445,446] It accounts for 1 to 12 cases per 10,000 hospitalizations and an incidence of 10 per 100,000 persons. Almost all cases are in males, particularly between the ages of 40 to 60 years. Bacteria are most often introduced through trauma or accidental percutaneous punctures and, very rarely, through intrabursal injection of corticosteroids or hematogenous dissemination.[445–449] Septic olecranon bursitis is four times more likely than septic prepatellar bursitis. Infection of deep bursae is rare and is usually secondary to contiguous spread from an adjacent joint infection.

More than 80% of septic bursitis is due to *S. aureus,* with the remainder due to *Streptococcus* spp. and various gram-negative bacteria, mycobacteria, and fungi.[445,447,448,450,451] Olecranon septic bursitis caused by the algal agent *Prototheca* has been reported (see Chapter 268).[445,452,453] Of note, infectious bursitis is more common during the summer months, especially that caused by *S. aureus*.

FIG. 103.8 Septic olecranon bursitis due to *Staphylococcus aureus.*

Patients with superficial bursitis present with painful swelling, redness, and increased warmth of the afflicted bursae (Fig. 103.8).[445,454] Evidence of an overlying cutaneous injury or lesion is often evident. Unlike septic arthritis, range of motion in the joint is not very restricted. However, in moderate or severe cases, pain may be extreme and the range of motion of the underlying joint reduced. Soft tissue edema and erythema may extend along the extremity and circumferentially about the joint. Associated systemic symptoms potentially include fever, chills, and malaise. Noninfectious causes of bursitis, especially that involving the olecranon bursa, can occur in conjunction with several systemic conditions, such as RA, gout, pseudogout, chondrocalcinosis, and pigmented villonodular synovitis, and must be differentiated from septic bursitis.[454] Sterile traumatic bursitis usually involves the prepatellar bursa and presents with a paucity of systemic symptoms.

The diagnosis of septic bursitis is made by aspirating the affected bursae and analyzing the fluid for WBC count and crystals. The WBC count threshold for a presumptive diagnosis of septic bursitis is greater than 1000 cells/mm^3 and is much lower than that for septic arthritis.[454] Gram staining and culture should also be performed. For chronic septic bursitis, mycobacterial and fungal smear and culture are indicated. To distinguish septic olecranon bursitis from acute arthritis of the elbow, it is helpful to evaluate whether pain is worsened by elbow extension versus flexion. Bursal pressures are increased in the latter case. Thus, for patients with septic bursitis, elbow pain is increased with joint flexion, whereas for patients with septic arthritis, synovial pressures are increased during elbow joint extension, and pain is greatest in this position.[448] Arthrocentesis should be performed if there is suspicion of joint involvement. Imaging with MRI or CT, followed by directed needle aspiration, is necessary to evaluate patients for deep bursal infection.

Treatment for septic bursitis includes antibiotics and daily aspiration of the bursae until sterile fluid is obtained.[446,454–457] In some acute cases bursectomy may be required. Antimicrobial selection should be based on bursal aspirate Gram stain as outlined in Table 103.5. Oral antimicrobials with antistaphylococcal activity are initially indicated for mild cases afflicting healthy patients with good access to medical care. Because of the high prevalence of CA-MRSA in many localities, clindamycin, TMP-SMX, and minocycline are appropriate choices because of their reliable activity against this pathogen. For more severe cases, or patients with chronic illness or immunosuppression, IV antimicrobials should be selected. In both cases definitive antibiotic therapy should be selected based on the identity and susceptibilities of cultured bacteria and continued to complete a 14- to 21-day course. The prognosis of prepatellar or olecranon septic bursitis is generally quite good, although recurrences are common and may require bursectomy when infection is quiescent.

Key References

The complete reference list is available online at Expert Consult.

4. Rutherford AI, Subesinghe S, Bharucha T, et al. A population study of the reported incidence of native joint septic arthritis in the United Kingdom between 1998 and 2013. *Rheumatology*. 2016;55:2176–2180.
5. Kennedy N, Chambers ST, Nolan I, et al. Native joint septic arthritis: epidemiology, clinical features, and microbiological causes in a New Zealand Population. *J Rheumatol*. 2015;42:2392–2397.
6. Nolla JM, Lora-Tamayo J, Vaquero CG, et al. Pyogenic arthritis of native joints in non-intravenous drug users: a detailed analysis of 268 cases attended in a tertiary hospital over a 22-year period. *Semin Arthritis Rheum*. 2015;45:94–102.
11. Andreasen RA, Andersen NS, Christensen R, et al. Prognostic factors associated with mortality in patients with septic arthritis: a descriptive cohort study. *Scand J Rheumatol*. 2017;46:27–32.
21. Murillo O, Grau I, Lora-Tamayo J, et al. The changing epidemiology of bacteraemic osteoarticular infections in the early 21st century. *Clin Microbiol Infect*. 2015;21:254.e1–254.e8.
22. Lim SY, Lu N, Choi HK. Septic arthritis in gout patients: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54:2095–2099.
28. Gobbi A, Karnatzikos G, Chaurasia S, et al. Postoperative infection after anterior cruciate ligament reconstruction. *Sports Health*. 2016;8:187–189.
29. Bauer T, Boisrenoult P, Jenny J-Y. Post–arthroscopy septic arthritis: current data and practical recommendations. *Orthop Traumatol Surg Res*. 2015;101:S347–S350.
31. Pauzenberger L, Grieb A, Hexel M, et al. Infections following arthroscopic rotator cuff repair: incidence, risk factors, and prophylaxis. *Knee Surg Sports Traumatol Arthrosc*. 2017;25:595–601.
39. Cecconi M, Ranza R, Titton DC, et al. Incidence of infectious adverse events in patients with rheumatoid arthritis and spondyloarthritis on biologic drugs—data from the Brazilian Registry for Biologics Monitoring. *J Clin Rheumatol*. 2018 [Epub ahead of print].
63. Boff D, Crijins H, Teixeira MM, et al. Neutrophils: beneficial and harmful cells in septic arthritis. *Int J Mol Sci*. 2018;19:468–496.
65. Ali A, Na M, Svensson MND, et al. IL-1 receptor antagonist treatment aggravates staphylococcal septic arthritis and sepsis in mice. *PLoS ONE*. 2015;10:e0131645.
71. Belkhir L, Rodriguez-Villalobos H, Vandercam B, et al. Pneumococcal septic arthritis in adults: clinical analysis and review. *Acta Clin Belg*. 2014;69:40–46.
73. Dubost JJ, Couderc M, Tatar Z, et al. Three-decade trends in the distribution of organisms causing septic arthritis in native joints: single-center study of 374 cases. *Joint Bone Spine*. 2014;8:438–440.
78. Lin WT, Wu CD, Cheng SC, et al. High prevalence of methicillin-resistant *Staphylococcus aureus* among patients with septic arthritis caused by *Staphylococcus aureus*. *PLoS ONE*. 2015;10:e0127150.
80. Jinno S, Sulis CA, Dubreuil MD. Causative pathogens, antibiotic susceptibility, and characteristics of patients with bacterial septic arthritis over time. *J Rheumatol*. 2018;45:725–726.
86. Bouras D, Doudoulakakis A, Tsolia M, et al. *Staphylococcus aureus* osteoarticular infections in children: an 8-year review of molecular microbiology, antibiotic resistance and clinical characteristics. *J Med Microbiol*. 2018;67:1753–1760.
87. Combs K, Cox K. Clinical outcomes involving patients that develop septic arthritis with methicillin sensitive *Staphylococcus aureus* versus methicillin-resistant *Staphylococcus aureus*. *J Orthop*. 2017;15:9–12.
91. Tan CD, Moritz D, Mena Lora AJ. *S. lugdunensis* native-joint septic arthritis: case report and review of the literature. *Case Rep Infect Dis*. 2017;2017:8903907.
96. Smith EM, Khan MA, Reingold A, et al. Group B *Streptococcus* infections of soft tissue and bone in California adults, 1995-2012. *Epidemiol Infect*. 2015;143:3343–3350.
101. García-País MJ, Rabuñal R, Armesto V, et al. *Streptococcus bovis* septic arthritis and osteomyelitis: a report of 21 cases and a literature review. *Semin Arthritis Rheum*. 2016;45:738–746.
104. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven gram-negative bacterial arthritis. *J Microbiol Immunol Infect*. 2017;50:527–531.
113. Yagupsky P. *Kingella kingae*: carriage, transmission, and disease. *Clin Microbiol Rev*. 2015;28:54–57.
117. Yagupsky P. Outbreaks of *Kingella kingae* infections in daycare facilities. *Emerg Infect Dis*. 2014;20:746–753.
121. Horneff JG 3rd, Hsu JE, Voleti PB, et al. *Propionibacterium acnes* infection in shoulder arthroscopy patients with postoperative pain. *J Shoulder Elbow Surg*. 2015;24:838–843.
122. Patzer T, Petersdorf S, Krauspe R, et al. Prevalence of *Propionibacterium acnes* in the glenohumeral compared with the subacromial space in primary shoulder arthroscopies. *J Shoulder Elbow Surg*. 2018;27:771–776.
147. Roberts J, Schaefer E, Gallo RA. Indicators for detection of septic arthritis in the acutely swollen joint cohort of those without joint prostheses. *Orthopedics*. 2014;37:e98–e102.
149. Deirmengian CA, Citrano PA, Gulati S, et al. The C-reactive protein may not detect infections caused by less-virulent organisms. *J Arthroplasty*. 2016;3:S152–S155.
150. Paosong S, Narongroeknawin P, Pakchotanon R, et al. Serum procalcitonin as a diagnostic aid in patients with acute bacterial septic arthritis. *Int J Rheum Dis*. 2015;18:352–359.
151. Shaikh MM, Hermans LE, van Laar JM. Is serum procalcitonin measurement a useful addition to a rheumatologist's repertoire? A review of its diagnostic role in systemic inflammatory diseases and joint infections. *Rheumatology*. 2015;54:231–240.
155. Ruzbarsky JJ, Gladnick BP, Dodwell E. Diagnosing septic arthritis in the synovial white cell count "Gray Zone". *HSS J*. 2016;12:190–192.
162. Bossard DA, Ledergerber B, Zingg PO, et al. Optimal length of cultivation time for isolation of *Propionibacterium acnes* in suspected bone and joint infections is more than 7 days. *J Clin Microbiol*. 2016;54:3043–3049.
163. Fowler ML, Zhu C, Byrne K, et al. Pathogen or contaminant? Distinguishing true infection from synovial fluid culture contamination in patients with suspected septic arthritis. *Infection*. 2017;45:825–830.
164. Frangiamore SJ, Saleh A, Grosso MJ, et al. Early versus late culture growth of *Propionibacterium acnes* in revision shoulder arthroplasty. *J Bone Joint Surg Am*. 2015;97:1149–1158.
167. Hernández-Rupérez MB, Suárez-Arrabal MDC, Villa-García Á, et al. *Kingella kingae* as the main cause of septic arthritis: importance of molecular diagnosis. *Pediatr Infect Dis J*. 2018;37:1211–1216.
168. Morgenstern C, Cabric S, Perka C, et al. Synovial fluid multiplex PCR is superior to culture for detection of low-virulent pathogens causing periprosthetic joint infection. *Diagn Microbiol Infect Dis*. 2018;90:115–119.
171. Morgenstern C, Renz N, Cabric S, et al. Multiplex polymerase chain reaction and microcalorimetry in synovial fluid: can pathogen-based detection assays improve the diagnosis of septic arthritis? *J Rheumatol*. 2018;45:1588–1593.
172. Pons B, Jay C, Marti T, et al. Identification of pathogens in synovial fluid samples with an automated multiplexed molecular detection system. *Open Forum Infect Dis*. 2018;5:S678–S679.
173. Simpfendorfer CS. Radiologic approach to musculoskeletal infections. *Infect Dis Clin N Am*. 2017;31:299–324.
181. Laine JC, Denning JR, Riccio AI, et al. The use of ultrasound in the management of septic arthritis of the hip. *J Pediatr Orthop B*. 2015;24:95–98.
185. Centers for Disease Control and Prevention. 2017 Sexually Transmitted Disease Surveillance: Gonorrhea. https://www.cdc.gov/std/stats17/gonorrhea.htm. Accessed October 31, 2018.
189. Sena Corrales G, Mora Navas L, Palacios Muñoz R, et al. Gonococcal arthritis in human immunodeficiency virus-infected patients. Review of the literature. *Reumatol Clin*. 2017;13:39–41.
194. Benavent Núñez D, Tornero Marín C, Bonilla Hernán G, et al. Gonococcal arthritis and C2 deficiency. *Reumatol Clin*. 2017;pii:S1699-258X(17)30234-6.
195. Davido B, Dinh A, Lagrange A, et al. Chronic gonococcal arthritis with C5 deficiency presenting with brief flare-ups: case study and literature review. *Clin Rheumatol*. 2014;33:1351–1353.
197. Crew PE, Abara WE, McCulley L, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. *Clin Infect Dis*. 2018 [Epub ahead of print].
202. Stein DC, LeVan A, Hardy B, et al. Expression of opacity proteins interferes with the transmigration of *Neisseria gonorrhoeae* across polarized epithelial cells. *PLoS ONE*. 2015;10:e0134342.
220. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD. 2017.
221. Miller AC, Polgreen PM. Many opportunities to record, diagnose, or treat injection drug-related infections are missed: a population-based cohort study of inpatient and emergency department settings. *Clin Infect Dis*. 2018 [Epub ahead of print].
222. Oh DHW, Wurcel AG, Tybor DJ, et al. Increased mortality and reoperation rates after treatment for septic arthritis of the knee in people who inject drugs: nationwide inpatient sample, 2000-2013. *Clin Orthop Relat Res*. 2018;476:1557–1565.
228. Section J, Gibbons SD, Barton T, et al. Microbiological culture methods for pediatric musculoskeletal infection: a guideline for optimal use. *J Bone Joint Surg Am*. 2015;97:441–449.
231. Colaco C, Dotel R. Coexisting polyarticular septic arthritis, gout and pseudogout. *BMJ Case Rep*. 2018;2018:pii:bcr-2018-226810.
234. Schmitt SK. Reactive arthritis. *Infect Dis Clin North Am*. 2017;31:265–277.
237. Johns BP, Loewenthal MR, Dewar DC. Open compared with arthroscopic treatment of acute septic arthritis of the native knee. *J Bone Joint Surg Am*. 2017;99:499–505.
238. Bovonratwet P, Nelson SJ, Bellamkonda K, et al. Similar 30-day complications for septic knee arthritis treated with arthrotomy or arthroscopy: an American College of Surgeons national surgical quality improvement program analysis. *Arthroscopy*. 2018;34:213–219.
240. de Sa D, Cargnelli S, Catapano M, et al. Efficacy of hip arthroscopy for the management of septic arthritis: a systematic review. *Arthroscopy*. 2015;31:1358–1370.
241. Dave OH, Patel KA, Andersen CR, et al. Surgical procedures needed to eradicate infection in knee septic arthritis. *Orthopedics*. 2016;39:50–54.
243. Memon M, Kay J, Ginsberg L, et al. Arthroscopic management of septic arthritis of the native shoulder joint. *Arthroscopy*. 2018;34:625–646.
245. Aim F, Delambre J, Bauer T, et al. Efficacy of arthroscopic treatment for resolving infection in septic arthritis of native joints. *Orthop Traumatol Surg Res*. 2015;101:61–64.
246. Hunter JG, Gross JM, Dahl JD, et al. Risk factors for failure of a single surgical debridement in adults with acute septic arthritis. *J Bone Joint Surg Am*. 2015;97:558–564.
247. Daynes J, Roth MF, Zekaj M, et al. Adult native septic arthritis in an inner city hospital: effects on length of stay. *Orthopedics*. 2016;39:e674–e679.
251. Neely MN, Kato L, Youn G, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62:1–12.
252. Hermsen ED, Mendez-Vigo L, Berbari EF, et al. A retrospective study of outcomes of device-associated osteomyelitis treated with daptomycin. *BMC Infect Dis*. 2016;16:310–313.
253. Malizos K, Sarma J, Seaton RA, et al. Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry. *Eur J Clin Microbiol Infect Dis*. 2016;35:111–118.
259. Roux S, Valour F, Karsenty J, et al. Daptomycin > 6 mg/kg/day as salvage therapy in patients with complex bone and joint infection: cohort study in a regional reference center. *BMC Infect Dis*. 2016;16:83.
260. Chang YJ, Lee MS, Lee CH, et al. Daptomycin treatment in patients with resistant staphylococcal periprosthetic joint infection. *BMC Infect Dis*. 2017;17:736.
261. Schrank GM, Wright SB, Branch-Elliman W, et al. A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy. *Infect Control Hosp Epidemiol*. 2018;39:947–954.
269. Pfaller MA, Flamm RK, Castanheira M, et al. Dalbavancin in-vitro activity obtained against Gram-positive clinical isolates causing bone and joint infections in US and European hospitals (2011-2016). *Int J Antimicrob Agents*. 2018;51:608–611.
270. Dunne MW, Puttagunta S, Sprenger CR, et al. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother*. 2015;59:1849–1855.
271. Bouza E, Valerio M, Soriano A, et al. Dalbavancin in the treatment of different gram-positive infections: a real-life experience. *Int J Antimicrob Agents*. 2018;51:571–577.
272. Ramírez Hidalgo M, Jover-Sáenz A, García-González M, et al. Dalbavancin treatment of prosthetic knee infection due to oxacillin-resistant *Staphylococcus epidermidis*. *Enferm Infecc Microbiol Clin*. 2018;36:142–143.
273. Malandain D, Dinh A, Ferry T, et al. Salvage therapy for complex bone and joint infections with ceftaroline: a multicentre, observational study. *Int J Antimicrob Agents*. 2017;50:277–280.
277. Workowski KA, Bolan G. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR–3):1–138.

279. Meier R, Wirth T, Hahn F, et al. Pyogenic arthritis of the fingers and the wrist: can we shorten antimicrobial treatment duration? *Open Forum Infect Dis*. 2017;4:ofx058.
281. Fogel I, Amir J, Bar-On E, et al. Dexamethasone therapy for septic arthritis in children. *Pediatrics*. 2015;136:e776–e782.
282. Qin YF, Li ZJ, Li H. Corticosteroids as adjunctive therapy with antibiotics in the treatment of children with septic arthritis: a meta-analysis. *Drug Des Devel Ther*. 2018;12:2277–2284.
283. Farrow L. A systematic review and meta-analysis regarding the use of corticosteroids in septic arthritis. *BMC Musculoskelet Disord*. 2015;16:241.
303. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med*. 2015;372:1231–1239.
304. McFee RB. Selected mosquito-borne illnesses–chikungunya. *Dis Mon*. 2018;64:222–234.
307. Centers for Disease Control and Prevention. Chikungunya Geographic Distribution. https://www.cdc.gov/chikungunya/geo/index.html. Accessed November 15, 2018.
311. Paixão ES, Rodrigues LC, Costa MDCN, et al. Chikungunya chronic disease: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2018;112:301–316.
314. Rosario V, Munoz-Louis R, Valdez T, et al. Chikungunya infection in the general population and in patients with rheumatoid arthritis on biological therapy. *Clin Rheumatol*. 2015;34:1285–1287.
330. Amissah-Arthur MB, Poller B, Tunbridge A, et al. Musculoskeletal manifestations of Ebola virus. *Rheumatology (Oxford)*. 2018;57:28–31.
331. Vetter P, Kaiser L, Schibler M, et al. Sequelae of Ebola virus disease: the emergency within the emergency. *Lancet Infect Dis*. 2016;16:e82–e91.
333. Chaussade H, Lebeaux D, Gras G, et al. *Nocardia* arthritis: 3 cases and literature review. *Medicine (Baltimore)*. 2015;94:e1671.
335. Henry MW, Miller AO, Walsh TJ, et al. Fungal musculoskeletal infections. *Infect Dis Clin North Am*. 2017;31:353–368.
340. Hospenthal D, Bennett J. Miscellaneous fungi and *Prototheca*. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia: Churchill Livingstone; 2000:2772–2780.
344. Gamaletsou MN, Rammaert B, Bueno MA, et al. *Candida* arthritis: analysis of 112 pediatric and adult cases. *Open Forum Infect Dis*. 2015;3:ofv207.
355. Zhou HX1, Lu L1, Chu T, et al. Skeletal cryptococcosis from 1977-2013. *Front Microbiol*. 2015;5:740.
358. Galgiani J. *Coccidioides immitis*. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Churchill Livingstone; 2015:2974–2984.
387. Taj-Aldeen SJ, Gamaletsou MN, Rammaert B, et al. Bone and joint infections caused by mucormycetes: a challenging osteoarticular mycosis of the twenty-first century. *Med Mycol*. 2017;55:691–704.
388. Taj-Aldeen SJ, Rammaert B, Gamaletsou M, et al. Osteoarticular infections caused by non-*Aspergillus* filamentous fungi in adult and pediatric patients: a systematic review. *Medicine (Baltimore)*. 2015;94:e2078.
399. Revankar SG, Baddley JW, Chen SC, et al. A Mycoses Study Group international prospective study of phaeohyphomycosis: an analysis of 99 proven/probable cases. *Open Forum Infect Dis*. 2017;4:ofx200.
400. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;61:1558–1565.
401. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–e50.
406. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63:e112–e146.
408. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1–e60.
413. Hogan JI, Hurtado RM, Nelson SB. Mycobacterial musculoskeletal infections. *Infect Dis Clin North Am*. 2017;31:369–382.
416. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
426. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:e1–e33.
428. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
432. Riera J, Conesa X, Pisa J, et al. Septic arthritis caused by *Mycobacterium marinum*. *Arch Orthop Trauma Surg*. 2016;136:131–134.
437. Fukui S, Sekiya N, Takizawa Y, et al. Disseminated *Mycobacterium abscessus* infection following septic arthritis. *Medicine (Baltimore)*. 2015;94:e861.
447. Reilly D, Kamineni S. Olecranon bursitis. *J Shoulder Elbow Surg*. 2016;25:158–167.
453. Know J, Coloe S, Perera C, et al. *Prototheca wickerhamii* olecranon bursitis successfully treated with adjunctive systemic itraconazole. *Pathology*. 2015;47:388–390.

References

1. Kaandorp CJ, van Schaardenburg D, Krijnen P, et al. Risk factors for septic arthritis in patients with joint disease. A prospective study. *Arthritis Rheum*. 1995;38:1819–1825.
2. Kaandorp CJ, Dinant HJ, van de Laar MA, et al. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. *Ann Rheum Dis*. 1997;56:470–475.
3. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology (Oxford)*. 2001;40:24–30.
4. Rutherford AI, Subesinghe S, Bharucha T, et al. A population study of the reported incidence of native joint septic arthritis in the United Kingdom between 1998 and 2013. *Rheumatology*. 2016;55:2176–2180.
5. Kennedy N, Chambers ST, Nolan I, et al. Native joint septic arthritis: epidemiology, clinical features, and microbiological causes in a New Zealand Population. *J Rheumatol*. 2015;42:2392–2397.
6. Nolla JM, Lora-Tamayo J, Vaquero CG, et al. Pyogenic arthritis of native joints in non-intravenous drug users: a detailed analysis of 268 cases attended in a tertiary hospital over a 22-year period. *Semin Arthritis Rheum*. 2015;45:94–102.
7. Favero M, Schiavon F, Riato L, et al. Rheumatoid arthritis is the major risk factor for septic arthritis in rheumatological settings. *Autoimmun Rev*. 2008;8: 59–61.
8. Morgan DS, Fisher D, Merianos A, et al. An 18-year clinical review of septic arthritis from tropical Australia. *Epidemiol Infect*. 1996;117:423–428.
9. Jeng GW, Wang CR, Liu ST, et al. Measurement of synovial tumor necrosis factor-alpha in diagnosing emergency patients with bacterial arthritis. *Am J Emerg Med*. 1997;15:626–629.
10. Shmerling RH, Delbanco TL, Tosteson AN, et al. Synovial fluid tests. What should be ordered? *JAMA*. 1990;264:1009–1014.
11. Andreasen RA, Andersen NS, Christensen R, et al. Prognostic factors associated with mortality in patients with septic arthritis: a descriptive cohort study. *Scand J Rheumatol*. 2017;46:27–32.
12. Weston VC, Jones AC, Bradbury N, et al. Clinical features and outcome of septic arthritis in a single UK Health District, 1982-1991. *Ann Rheum Dis*. 1999;58:214–219.
13. Kaandorp CJE, Krijnen P, Moens HJB, et al. The outcome of bacterial arthritis: a prospective community-based study. *Arthritis Rheum*. 1997;40:884–892.
14. Dubost JJ, Fis I, Denis P, et al. Polyarticular septic arthritis. *Medicine (Baltimore)*. 1993;72:296–310.
15. Fangtham M, Baer AN. Methicillin-resistant *Staphylococcus aureus* arthritis in adults: case report and review of the literature. *Semin Arthritis Rheum*. 2012;41:604–610.
16. Lipsky BA, Weigelt JA, Gupta V, et al. Skin, soft tissue, bone, and joint infections in hospitalized patients: epidemiology and microbiological, clinical, and economic outcomes. *Infect Control Hosp Epidemiol*. 2007;28:1290–1298.
17. Gupta MN, Sturrock RD, Field M. Prospective comparative study of patients with culture proven and high suspicion of adult onset septic arthritis. *Ann Rheum Dis*. 2003;62:327–331.
18. Goldenberg DL, Reed JI. Bacterial arthritis. *N Engl J Med*. 1985;312:764–771.
19. Sapico FL, Liquete JA, Sarma RJ. Bone and joint infections in patients with infective endocarditis: review of a 4-year experience. *Clin Infect Dis*. 1996;22:783–787.
20. Goldenberg DL. Septic arthritis. *Lancet*. 1998;351:197–202.
21. Murillo O, Grau I, Lora-Tamayo J, et al. The changing epidemiology of bacteraemic osteoarticular infections in the early 21st century. *Clin Microbiol Infect*. 2015;21:254.e1–254.e8.
22. Lim SY, Lu N, Choi HK. Septic arthritis in gout patients: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54:2095–2099.
23. Shirtliff ME, Mader JT. Acute septic arthritis. *Clin Microbiol Rev*. 2002;15:527–544.
24. Mathews CJ, Weston VC, Jones A, et al. Bacterial septic arthritis in adults. *Lancet*. 2010;375:846–855.
25. Clerc O, Prod'hom G, Greub G, et al. Adult native septic arthritis: a review of 10 years of experience and lessons for empirical antibiotic therapy. *J Antimicrob Chemother*. 2011;66:1168–1173.
26. Rodriguez CL, Ferran NA, Lyons K, et al. Bilateral glenohumeral septic arthritis secondary to retroperitoneal abscess. *Bull NYU Hosp Jt Dis*. 2009;67:378–380.
27. Messieh M, Turner R, Bunch F, et al. Hip sepsis from retroperitoneal rupture of diverticular disease. *Orthop Rev*. 1993;22:597–599.
28. Gobbi A, Karnatzikos G, Chaurasia S, et al. Postoperative infection after anterior cruciate ligament reconstruction. *Sports Health*. 2016;8:187–189.
29. Bauer T, Boisrenoult P, Jenny J-Y. Post–arthroscopy septic arthritis: current data and practical recommendations. *Orthop Traumatol Surg Res*. 2015;101:S347–S350.
30. Wang C, Ao Y, Wang J, et al. Septic arthritis after arthroscopic anterior cruciate ligament reconstruction: a retrospective analysis of incidence, presentation, treatment, and cause. *Arthroscopy*. 2009;25:243–249.
31. Pauzenberger L, Grieb A, Hexel M, et al. Infections following arthroscopic rotator cuff repair: incidence, risk factors, and prophylaxis. *Knee Surg Sports Traumatol Arthrosc*. 2017;25:595–601.
32. Nallamshetty L, Buchowski JM, Nazarian LA, et al. Septic arthritis of the hip following cortisone injection: case report and review of the literature. *Clin Imaging*. 2003;27:225–228.
33. Centers for Disease Control and Prevention. *Exophiala* infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July-November 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51:1109–1112.
34. Smith RM, Schaefer MK, Kainer MA, et al. Fungal infections associated with contaminated methylprednisolone injections—preliminary report. *N Engl J Med*. 2012;369:1598–1609.
35. Al-Nammari SS, Gulati V, Patel R, et al. Septic arthritis in haemodialysis patients: a seven-year multi-centre review. *J Orthop Surg (Hong Kong)*. 2008;16:54–57.
36. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. *Arthritis Rheum*. 2007;57:1151–1157.
37. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2006;54:2368–2376.
38. Giles JT, Bartlett SJ, Gelber AC, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. *Arthritis Rheum*. 2006;55:333–337.
39. Cecconi M, Ranza R, Titton DC, et al. Incidence of infectious adverse events in patients with rheumatoid arthritis and spondyloarthritis on biologic drugs—data from the Brazilian Registry for Biologics Monitoring. *J Clin Rheumatol*. 2018 [Epub ahead of print].
40. Strangfeld A, Listing J. Infection and musculoskeletal conditions: bacterial and opportunistic infections during anti-TNF therapy. *Best Pract Res Clin Rheumatol*. 2006;20:1181–1195.
41. Schett G, Herak P, Graninger W, et al. *Listeria*-associated arthritis in a patient undergoing etanercept therapy: case report and review of the literature. *J Clin Microbiol*. 2005;43:2537–2541.
42. Galloway JB, Hyrich KL, Mercer LK, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2011;70:1810–1814.
43. Saraux A, Taelman H, Blanche P, et al. HIV infection as a risk factor for septic arthritis. *Br J Rheumatol*. 1997;36:333–337.
44. Zalavras CG, Dellamaggiora R, Patzakis MJ, et al. Septic arthritis in patients with human immunodeficiency virus. *Clin Orthop Relat Res*. 2006;451:46–49.
45. Vassilopoulos D, Chalasani P, Jurado RL, et al. Musculoskeletal infections in patients with human immunodeficiency virus infection. *Medicine (Baltimore)*. 1997;76:284–294.
46. Ventura G, Gasparini G, Lucia MB, et al. Osteoarticular bacterial infections are rare in HIV-infected patients. 14 cases found among 4,023 HIV-infected patients. *Acta Orthop Scand*. 1997;68:554–558.
47. Belzunegui J, Gonzalez C, Lopez L, et al. Osteoarticular and muscle infectious lesions in patients with the human immunodeficiency virus. *Clin Rheumatol*. 1997;16:450–453.
48. Margaretten ME, Kohlwes J, Moore D, et al. Does this adult patient have septic arthritis? *JAMA*. 2007;297: 1478–1488.
49. Carpenter CR, Schuur JD, Everett WW, et al. Evidence-based diagnostics: adult septic arthritis. *Acad Emerg Med*. 2011;18:781–796.
50. Tarkowski A. Infection and musculoskeletal conditions: infectious arthritis. *Best Pract Res Clin Rheumatol*. 2006;20:1029–1044.
51. Tarkowski A, Collins LV, Gjertsson I, et al. Model systems: modeling human staphylococcal arthritis and sepsis in the mouse. *Trends Microbiol*. 2001;9:321–326.
52. Jonsson IM, Pietrocola G, Speziale P, et al. Role of fibrinogen-binding adhesin expression in septic arthritis and septicemia caused by *Streptococcus agalactiae*. *J Infect Dis*. 2005;192:1456–1464.
53. Fischer B, Vaudaux P, Magnin M, et al. Novel animal model for studying the molecular mechanisms of bacterial adhesion to bone-implanted metallic devices: role of fibronectin in *Staphylococcus aureus* adhesion. *J Orthop Res*. 1996;14:914–920.
54. Ryden C, Tung HS, Nikolaev V, et al. *Staphylococcus aureus* causing osteomyelitis binds to a nonapeptide sequence in bone sialoprotein. *Biochem J*. 1997;327 (Pt 3):825–829.
55. Shaw LN, Lindholm C, Prajsnar TK, et al. Identification and characterization of sigma, a novel component of the *Staphylococcus aureus* stress and virulence responses. *PLoS ONE*. 2008;3:e3844.
56. Camargo IL, Gilmore MS. *Staphylococcus aureus*—probing for host weakness? *J Bacteriol*. 2008;190: 2253–2256.
57. Kehl-Fie TE, Porsch EA, Yagupsky P, et al. Examination of type IV pilus expression and pilus-associated phenotypes in *Kingella kingae* clinical isolates. *Infect Immun*. 2010;78:1692–1699.
58. Kehl-Fie TE, St Geme JW 3rd. Identification and characterization of an RTX toxin in the emerging pathogen *Kingella kingae*. *J Bacteriol*. 2007;189: 430–436.
59. Deng GM, Tarkowski A. The features of arthritis induced by CpG motifs in bacterial DNA. *Arthritis Rheum*. 2000;43:356–364.
60. Palmqvist N, Foster T, Tarkowski A, et al. Protein A is a virulence factor in *Staphylococcus aureus* arthritis and septic death. *Microb Pathog*. 2002;33:239–249.
61. Puliti M, Momi S, Falcinelli E, et al. Contribution of matrix metalloproteinase 2 to joint destruction in group B *Streptococcus*-induced murine arthritis. *Arthritis Rheum*. 2012;64:1089–1097.
62. Mader JT, Shirtliff M, Calhoun JH. The host and the skeletal infection: classification and pathogenesis of acute bacterial bone and joint sepsis. *Baillieres Best Pract Res Clin Rheumatol*. 1999;13:1–20.
63. Boff D, Crijins H, Teixeira MM, et al. Neutrophils: beneficial and harmful cells in septic arthritis. *Int J Mol Sci*. 2018;19:468–496.
64. Goldenberg DL, Chisholm PL, Rice PA. Experimental models of bacterial arthritis: a microbiologic and histopathologic characterization of the arthritis after the intraarticular injections of *Neisseria gonorrhoeae, Staphylococcus aureus,* group A streptococci, and *Escherichia coli*. *J Rheumatol*. 1983;10:5–11.
65. Ali A, Na M, Svensson MND, et al. IL-1 Receptor antagonist treatment aggravates staphylococcal septic arthritis and sepsis in mice. *PLoS ONE*. 2015;10:e0131645.
66. Roy S, Bhawan J. Ultrastructure of articular cartilage in pyogenic arthritis. *Arch Pathol*. 1975;99:44–47.
67. Gardner GC, Weisman MH. Pyarthrosis in patients with rheumatoid arthritis: a report of 13 cases and a review of the literature from the past 40 years. *Am J Med*. 1990;88:503–511.
68. Rosenthal J, Bole GG, Robinson WD. Acute nongonococcal infectious arthritis. Evaluation of risk factors, therapy, and outcome. *Arthritis Rheum*. 1980;23:889–897.
69. Dubost JJ, Soubrier M, De Champs C, et al. No changes in the distribution of organisms responsible for septic arthritis over a 20-year period. *Ann Rheum Dis*. 2002;61:267–269.
70. Ross JJ, Saltzman CL, Carling P, et al. Pneumococcal septic arthritis: review of 190 cases. *Clin Infect Dis*. 2003;36:319–327.
71. Belkhir L, Rodriguez-Villalobos H, Vandercam B, et al. Pneumococcal septic arthritis in adults: clinical analysis and review. *Acta Clin Belg*. 2014;69:40–46.
72. Ryan MJ, Kavanagh R, Wall PG, et al. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four year period. *Br J Rheumatol*. 1997;36:370–373.
73. Dubost JJ, Couderc M, Tatar Z, et al. Three-decade trends in the distribution of organisms causing septic arthritis in native joints: single-center study of 374 cases. *Joint Bone Spine*. 2014;8:438–440.
74. Goldenberg DL. Infectious arthritis complicating rheumatoid arthritis and other chronic rheumatic disorders. *Arthritis Rheum*. 1989;32:496–502.
75. Frazee BW, Fee C, Lambert L. How common is MRSA in adult septic arthritis? *Ann Emerg Med*. 2009;54: 695–700.
76. Okano T, Enokida M, Otsuki R, et al. Recent trends in adult-onset septic arthritis of the knee and hip: retrospective analysis of patients treated during the past 50 years. *J Infect Chemother*. 2011;17:666–670.

77. Huang SS, Platt R. Risk of methicillin-resistant *Staphylococcus aureus* infection after previous infection or colonization. *Clin Infect Dis*. 2003;36:281–285.
78. Lin WT, Wu CD, Cheng SC, et al. High Prevalence of methicillin-resistant *Staphylococcus aureus* among patients with septic arthritis caused by *Staphylococcus aureus*. *PLoS ONE*. 2015;10:e0127150.
79. Ross JJ, Davidson L. Methicillin-resistant *Staphylococcus aureus* septic arthritis: an emerging clinical syndrome. *Rheumatology (Oxford)*. 2005;44:1197–1198.
80. Jinno S, Sulis CA, Dubreuil MD. Causative pathogens, antibiotic susceptibility, and characteristics of patients with bacterial septic arthritis over time. *J Rheumatol*. 2018;45:725–726.
81. Kini AR, Shetty V, Kumar AM, et al. Community-associated, methicillin-susceptible, and methicillin-resistant *Staphylococcus aureus* bone and joint infections in children: experience from India. *J Pediatr Orthop B*. 2013;22:158–166.
82. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *J Pediatr Orthop*. 2006;26:703–708.
83. Gwynne-Jones DP, Stott NS. Community-acquired methicillin-resistant *Staphylococcus aureus*: a cause of musculoskeletal sepsis in children. *J Pediatr Orthop*. 1999;19:413–416.
84. Kallarackal G, Lawson TM, Williams BD. Community-acquired septic arthritis due to methicillin-resistant *Staphylococcus aureus*. *Rheumatology (Oxford)*. 2000;39:1304–1305.
85. Martinez-Aguilar G, Avalos-Mishaan A, Hulten K, et al. Community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* musculoskeletal infections in children. *Pediatr Infect Dis J*. 2004;23:701–706.
86. Bouras D, Doudoulakakis A, Tsolia M, et al. *Staphylococcus aureus* osteoarticular infections in children: an 8-year review of molecular microbiology, antibiotic resistance and clinical characteristics. *J Med Microbiol*. 2018;67:1753–1760.
87. Combs K, Cox K. Clinical outcomes involving patients that develop septic arthritis with methicillin sensitive *Staphylococcus aureus* versus methicillin-resistant *Staphylococcus aureus*. *J Orthop*. 2017;15:9–12.
88. Wang WY, Lee SY, Chiueh TS, et al. Molecular and phenotypic characteristics of methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus* isolates from patients with septic arthritis. *J Clin Microbiol*. 2009;47:3617–3623.
89. Lu JJ, Lee SY, Hwa SY, et al. Septic arthritis caused by vancomycin-intermediate *Staphylococcus aureus*. *J Clin Microbiol*. 2005;43:4156–4158.
90. Fridkin SK, Hageman J, McDougal LK, et al. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997-2001. *Clin Infect Dis*. 2003;36:429–439.
91. Tan CD, Moritz D, Mena Lora AJ. *S. lugdunensis* native-joint septic arthritis: case report and review of the literature. *Case Rep Infect Dis*. 2017;2017:8903907.
92. Park KH, Kim KH, Kang JH, et al. Current status and clinical presentations of invasive neonatal Group B streptococcal infections in Korea. *Pediatr Int*. 2011;53:236–239.
93. Dubost JJ, Soubrier M, De Champs C, et al. Streptococcal septic arthritis in adults. A study of 55 cases with a literature review. *Joint Bone Spine*. 2004;71:303–311.
94. Schattner A, Vosti KL. Bacterial arthritis due to beta-hemolytic streptococci of serogroups A, B, C, F, and G. Analysis of 23 cases and a review of the literature. *Medicine (Baltimore)*. 1998;77:122–139.
95. Nolla JM, Gomez-Vaquero C, Corbella X, et al. Group B *Streptococcus* (*Streptococcus agalactiae*) pyogenic arthritis in nonpregnant adults. *Medicine (Baltimore)*. 2003;82:119–128.
96. Smith EM, Khan MA, Reingold A, et al. Group B *Streptococcus* infections of soft tissue and bone in California adults, 1995-2012. *Epidemiol Infect*. 2015;143:3343–3350.
97. Lun ZR, Wang QP, Chen XG, et al. *Streptococcus suis:* an emerging zoonotic pathogen. *Lancet Infect Dis*. 2007;7:201–209.
98. Wangsomboonsiri W, Luksananun T, Saksornchai S, et al. *Streptococcus suis* infection and risk factors for mortality. *J Infect*. 2008;57:392–396.
99. Weinstein MR1, Litt M, Kertesz DA, et al. Invasive infections due to a fish pathogen, *Streptococcus iniae*. *S. iniae* Study Group. *N Engl J Med*. 1997;337:589–594.
100. Yombi J, Belkhir L, Jonckheere S, et al. *Streptococcus gordonii* septic arthritis: two cases and review of literature. *BMC Infect Dis*. 2012;12:215.
101. García-País MJ, Rabuñal R, Armesto V, et al. *Streptococcus bovis* septic arthritis and osteomyelitis: a report of 21 cases and a literature review. *Semin Arthritis Rheum*. 2016;45:738–746.
102. Gavet F, Tournadre A, Soubrier M, et al. Septic arthritis in patients aged 80 and older: a comparison with younger adults. *J Am Geriatr Soc*. 2005;53:1210–1213.
103. Schelenz S, Bramham K, Goldsmith D. Septic arthritis due to extended spectrum beta lactamase producing *Klebsiella pneumoniae*. *Joint Bone Spine*. 2007;74:275–278.
104. Lin WT, Tang HJ, Lai CC, et al. Clinical manifestations and bacteriological features of culture-proven gram-negative bacterial arthritis. *J Microbiol Immunol Infect*. 2017;50:527–531.
105. Garza-Castro S, Gonzalez-Rivera CE, Vilchez-Cavazos JF, et al. Septic knee arthritis caused by *Pseudomonas aeruginosa* after anterior cruciate ligament reconstruction in an adolescent athlete. *Acta Ortop Mex*. 2012;26:53–56, [in Spanish].
106. Seyman D, Ozen NS, Inan D, et al. *Pseudomonas aeruginosa* septic arthritis of knee after intra-articular ozone injection. *New Microbiol*. 2012;35:345–348.
107. Hermet M, Minichiello E, Flipo RM, et al. Infectious sacroiliitis: a retrospective, multicentre study of 39 adults. *BMC Infect Dis*. 2012;12:305.
108. To F, Tam P, Villanyi D. Septic arthritis of the pubic symphysis from *Pseudomonas aeruginosa*: reconsidering traditional risk factors and symptoms in the elderly patient. *BMJ Case Rep*. 2012.
109. Ross JJ, Hu LT. Septic arthritis of the pubic symphysis: review of 100 cases. *Medicine (Baltimore)*. 2003;82:340–345.
110. Ross JJ, Shamsuddin H. Sternoclavicular septic arthritis: review of 180 cases. *Medicine (Baltimore)*. 2004;83:139–148.
111. Ohl C, Pollack M. *Pseudomonas aeruginosa* and related bacteria. In: Gorbach S, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. 3rd ed. New York: Lippincott Williams & Wilkins; 2004:1703–1707.
112. Bowerman SG, Green NE, Mencio GA. Decline of bone and joint infections attributable to *Haemophilus influenzae* type b. *Clin Orthop*. 1997;128-133.
113. Yagupsky P. *Kingella kingae:* carriage, transmission, and disease. *Clin Microbiol Rev*. 2015;28:54–57.
114. Dubnov-Raz G, Scheuerman O, Chodick G, et al. Invasive *Kingella kingae* infections in children: clinical and laboratory characteristics. *Pediatrics*. 2008;122:1305–1309.
115. Yagupsky P. *Kingella kingae*: from medical rarity to an emerging paediatric pathogen. *Lancet Infect Dis*. 2004;4:358–367.
116. Yagupsky P, Porsch E, St Geme JW. *Kingella kingae:* an emerging pathogen in young children. *Pediatrics*. 2011;127:557–565.
117. Yagupsky P. Outbreaks of *Kingella kingae* infections in daycare facilities. *Emerg Infect Dis*. 2014;20:746–753.
118. Centers for Disease Control and Prevention. Osteomyelitis/septic arthritis caused by *Kingella kingae* among day care attendees—Minnesota, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:241–243.
119. Bidet P, Collin E, Basmaci R, et al. Investigation of an outbreak of osteoarticular infections caused by *Kingella kingae* in a childcare center using molecular techniques. *Pediatr Infect Dis J*. 2013;32:558–560.
120. Brook I. Microbiology and management of joint and bone infections due to anaerobic bacteria. *J Orthop Sci*. 2008;13:160–169.
121. Horneff JG 3rd, Hsu JE, Voleti PB, et al. *Propionibacterium acnes* infection in shoulder arthroscopy patients with postoperative pain. *J Shoulder Elbow Surg*. 2015;24:838–843.
122. Patzer T, Petersdorf S, Krauspe R, et al. Prevalence of *Propionibacterium acnes* in the glenohumeral compared with the subacromial space in primary shoulder arthroscopies. *J Shoulder Elbow Surg*. 2018;27:771–776.
123. Brook I. Management of human and animal bite wound infection: an overview. *Curr Infect Dis Rep*. 2009;11:389–395.
124. Ewing R, Fainstein V, Musher DM, et al. Articular and skeletal infections caused by Pasteurella multocida. *South Med J*. 1980;73:1349–1352.
125. Murray PM. Septic arthritis of the hand and wrist. *Hand Clin*. 1998;14:579–587.
126. Resnick D, Pineda CJ, Weisman MH, et al. Osteomyelitis and septic arthritis of the hand following human bites. *Skeletal Radiol*. 1985;14:263–266.
127. Dendle C, Woolley IJ, Korman TM. Rat-bite fever septic arthritis: illustrative case and literature review. *Eur J Clin Microbiol Infect Dis*. 2006;25:791–797.
128. Wang TK, Wong SS. *Streptobacillus moniliformis* septic arthritis: a clinical entity distinct from rat-bite fever? *BMC Infect Dis*. 2007;7:56.
129. Kratz A, Greenberg D, Barki Y, et al. *Pantoea agglomerans* as a cause of septic arthritis after palm tree thorn injury; case report and literature review. *Arch Dis Child*. 2003;88:542–544.
130. Cooper C, Cawley MI. Bacterial arthritis in an English health district: a 10 year review. *Ann Rheum Dis*. 1986;45:458–463.
131. Dubost JJ, Soubrier M, Sauvezie B. Pyogenic arthritis in adults. *Joint Bone Spine*. 2000;67:11–21.
132. Smith JW, Hasan M. Infectious arthritis. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia: Churchill Livingstone; 2000:1175–1182.
133. Ledermann HP, Morrison WB, Schweitzer ME. MR image analysis of pedal osteomyelitis: distribution, patterns of spread, and frequency of associated ulceration and septic arthritis. *Radiology*. 2002;223:747–755.
134. Aglas F, Gretler J, Rainer F, et al. Sternoclavicular septic arthritis: a rare but serious complication of subclavian venous catheterization. *Clin Rheumatol*. 1994;13:507–512.
135. Robinson CM, Jenkins PJ, Markham PE, et al. Disorders of the sternoclavicular joint. *J Bone Joint Surg Br*. 2008;90:685–696.
136. Almoujahed MO, Khatib R, Baran J. Pregnancy-associated pyogenic sacroiliitis: case report and review. *Infect Dis Obstet Gynecol*. 2003;11:53–57.
137. Feldman LS. *Salmonella* septic sacroiliitis: case report and review. *Pediatr Infect Dis J*. 2006;25:187–189.
138. Osman AA, Govender S. Septic sacroiliitis. *Clin Orthop*. 1995;214–219.
139. Mancarella L, De Santis M, Magarelli N, et al. Septic sacroiliitis: an uncommon septic arthritis. *Clin Exp Rheumatol*. 2009;27:1004–1008.
140. Mulvey JM. Postpartum septic sacroiliitis coincident with labour epidural analgesia. *Anaesth Intensive Care*. 2008;36:875–878.
141. Avcu S, Mentes O, Bulut MD, et al. Sacroiliitis due to *Salmonella* Typhi: a case report. *N Am J Med Sci*. 2010;2:208–210.
142. Ariza J, Pujol M, Valverde J, et al. Brucellar sacroiliitis: findings in 63 episodes and current relevance. *Clin Infect Dis*. 1993;16:761–765.
143. Centers for Disease Control and Prevention. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy—United States, 2012. *MMWR Morb Mortal Wkly Rep*. 2012;61:839–842.
144. Vyskocil JJ, McIlroy MA, Brennan TA, et al. Pyogenic infection of the sacroiliac joint. Case reports and review of the literature. *Medicine (Baltimore)*. 1991;70:188–197.
145. Nade S. Septic arthritis. *Best Pract Res Clin Rheumatol*. 2003;17:183–200.
146. Mathews CJ, Kingsley G, Field M, et al. Management of septic arthritis: a systematic review. *Ann Rheum Dis*. 2007;66:440–445.
147. Roberts J, Schaefer E, Gallo RA. Indicators for detection of septic arthritis in the acutely swollen joint cohort of those without joint prostheses. *Orthopedics*. 2014;37:e98–e102.
148. Brennan MB, Hsu JL. Septic arthritis in the native joint. *Curr Infect Dis Rep*. 2012;14:558–565.
149. Deirmengian CA, Citrano PA, Gulati S, et al. The C-reactive protein may not detect infections caused by less-virulent organisms. *J Arthroplasty*. 2016;3:S152–S155.
150. Paosong S, Narongroeknawin P, Pakchotanon R, et al. Serum procalcitonin as a diagnostic aid in patients with acute bacterial septic arthritis. *Int J Rheum Dis*. 2015;18:352–359.
151. Shaikh MM, Hermans LE, van Laar JM. Is serum procalcitonin measurement a useful addition to a rheumatologist's repertoire? A review of its diagnostic role in systemic inflammatory diseases and joint infections. *Rheumatology*. 2015;54:231–240.
152. Shen CJ, Wu MS, Lin KH, et al. The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2013;32:807–814.
153. Sato H1, Tanabe N, Murasawa A, et al. Procalcitonin is a specific marker for detecting bacterial infection in patients with rheumatoid arthritis. *J Rheumatol*. 2012;39:1517–1523.
154. Hugle T, Schuetz P, Mueller B, et al. Serum procalcitonin for discrimination between septic and non-septic arthritis. *Clin Exp Rheumatol*. 2008;26:453–456.
155. Ruzbarsky JJ, Gladnick BP, Dodwell E. Diagnosing septic arthritis in the synovial white cell count "Gray Zone". *HSS J*. 2016;12:190–192.
156. Saeed K, Dryden M, Sitjar A, et al. Measuring synovial fluid procalcitonin levels in distinguishing cases of septic arthritis, including prosthetic joints, from other causes of arthritis and aseptic loosening. *Infection*. 2013;41:845–849.

157. Hughes JG, Vetter EA, Patel R, et al. Culture with BACTEC Peds Plus/F bottle compared with conventional methods for detection of bacteria in synovial fluid. *J Clin Microbiol*. 2001;39:4468–4471.
158. von Essen R. Culture of joint specimens in bacterial arthritis. Impact of blood culture bottle utilization. *Scand J Rheumatol*. 1997;26:293–300.
159. Kortekangas P, Aro HT, Lehtonen OP. Synovial fluid culture and blood culture in acute arthritis. A multi-case report of 90 patients. *Scand J Rheumatol*. 1995;24:44–47.
160. Yagupsky P, Peled N, Press J. Use of BACTEC 9240 blood culture system for detection of *Brucella melitensis* in synovial fluid. *J Clin Microbiol*. 2001;39:738–739.
161. Yagupsky P, Press J. Use of the isolator 1.5 microbial tube for culture of synovial fluid from patients with septic arthritis. *J Clin Microbiol*. 1997;35:2410–2412.
162. Bossard DA, Ledergerber B, Zingg PO, et al. Optimal length of cultivation time for isolation of *Propionibacterium acnes* in suspected bone and joint infections is more than 7 days. *J Clin Microbiol*. 2016;54:3043–3049.
163. Fowler ML, Zhu C, Byrne K, et al. Pathogen or contaminant? Distinguishing true infection from synovial fluid culture contamination in patients with suspected septic arthritis. *Infection*. 2017;45:825–830.
164. Frangiamore SJ, Saleh A, Grosso MJ, et al. Early versus late culture growth of *Propionibacterium acnes* in revision shoulder arthroplasty. *J Bone Joint Surg Am*. 2015;97:1149–1158.
165. Fenollar F, Levy PY, Raoult D. Usefulness of broad-range PCR for the diagnosis of osteoarticular infections. *Curr Opin Rheumatol*. 2008;20:463–470.
166. Yang S, Ramachandran P, Hardick A, et al. Rapid PCR-based diagnosis of septic arthritis by early Gram-type classification and pathogen identification. *J Clin Microbiol*. 2008;46:1386–1390.
167. Hernández-Rupérez MB, Suárez-Arrabal MDC, Villa-García Á, et al. *Kingella kingae* as the main cause of septic arthritis: importance of molecular diagnosis. *Pediatr Infect Dis J*. 2018;37:1211–1216.
168. Morgenstern C, Cabric S, Perka C, et al. Synovial fluid multiplex PCR is superior to culture for detection of low-virulent pathogens causing periprosthetic joint infection. *Diagn Microbiol Infect Dis*. 2018;90:115–119.
169. Fenollar F, Roux V, Stein A, et al. Analysis of 525 samples to determine the usefulness of PCR amplification and sequencing of the 16S rRNA gene for diagnosis of bone and joint infections. *J Clin Microbiol*. 2006;44:1018–1028.
170. Bonilla H, Kepley R, Pawlak J, et al. Rapid diagnosis of septic arthritis using 16S rDNA PCR: a comparison of 3 methods. *Diagn Microbiol Infect Dis*. 2011;69:390–395.
171. Morgenstern C, Renz N, Cabric S, et al. Multiplex polymerase chain reaction and microcalorimetry in synovial fluid: can pathogen-based detection assays improve the diagnosis of septic arthritis? *J Rheumatol*. 2018;45:1588–1593.
172. Pons B, Jay C, Marti T, et al. Identification of pathogens in synovial fluid samples with an automated multiplexed molecular detection system. *Open Forum Infect Dis*. 2018;5:S678–S679.
173. Simpfendorfer CS. Radiologic approach to musculoskeletal infections. *Infect Dis Clin N Am*. 2017;31:299–324.
174. Greenspan A, Tehranzadeh J. Imaging of infectious arthritis. *Radiol Clin North Am*. 2001;39:267–276.
175. Akkasilpa S, Osiri M, Ukritchon S, et al. Clinical features of septic arthritis of sternoclavicular joint. *J Med Assoc Thai*. 2001;84:63–68.
176. Coan MR, Demos TC, Lomasney L, et al. Radiologic case study. Pyogenic left sacroiliac infection. *Orthopedics*. 2002;25:197–200.
177. Learch TJ, Farooki S. Magnetic resonance imaging of septic arthritis. *Clin Imaging*. 2000;24:236–242.
178. Karchevsky M, Schweitzer ME, Morrison WB, et al. MRI findings of septic arthritis and associated osteomyelitis in adults. *AJR Am J Roentgenol*. 2004;182:119–122.
179. Bortolotto C, Gregoli B, Coscia DR, et al. Septic complications involving hand and wrist in patients with pre-existing rheumatoid arthritis: the role of magnetic resonance imaging and sonography. *J Ultrasound*. 2012;15:115–120.
180. Kim EY, Kwack KS, Cho JH, et al. Usefulness of dynamic contrast-enhanced MRI in differentiating between septic arthritis and transient synovitis in the hip joint. *AJR Am J Roentgenol*. 2012;198:428–433.
181. Laine JC, Denning JR, Riccio AI, et al. The use of ultrasound in the management of septic arthritis of the hip. *J Pediatr Orthop B*. 2015;24:95–98.
182. Bardin T. Gonococcal arthritis. *Best Pract Res Clin Rheumatol*. 2003;17:201–208.
183. Rice PA. Gonococcal arthritis (disseminated gonococcal infection). *Infect Dis Clin North Am*. 2005;19:853–861.
184. Centers for Disease Control and Prevention. 2011 Sexually Transmitted Disease Surveillance: Gonorrhea. http://www.cdc.gov/std/stats11/gonorrhea.htm. Accessed October 31, 2018.
185. Centers for Disease Control and Prevention. 2017 Sexually Transmitted Disease Surveillance: Gonorrhea. https://www.cdc.gov/std/stats17/gonorrhea.htm. Accessed October 31, 2018.
186. Cucurull E, Espinoza LR. Gonococcal arthritis. *Rheum Dis Clin North Am*. 1998;24:305–322.
187. O'Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. *Medicine (Baltimore)*. 1983;62:395–406.
188. Britigan BE, Cohen MS, Sparling PF. Gonococcal infection: a model of molecular pathogenesis. *N Engl J Med*. 1985;312:1683–1694.
189. Sena Corrales G, Mora Navas L, Palacios Muñoz R, et al. Gonococcal arthritis in human immunodeficiency virus-infected patients. Review of the literature. *Reumatol Clin*. 2017;13:39–41.
190. Masi AT, Eisenstein BI. Disseminated gonococcal infection (DGI) and gonococcal arthritis (GCA), II. Clinical manifestations, diagnosis, complications, treatment, and prevention. *Semin Arthritis Rheum*. 1981;10:173–197.
191. Zbella EA, Deppe G, Elrad H. Gonococcal arthritis in pregnancy. *Obstet Gynecol Surv*. 1984;39:8–12.
192. Joiner KA, Warren KA, Brown EJ, et al. Studies on the mechanism of bacterial resistance to complement-mediated killing. IV. C5b-9 forms high molecular weight complexes with bacterial outer membrane constituents on serum-resistant but not on serum-sensitive *Neisseria gonorrhoeae*. *J Immunol*. 1983;131:1443–1451.
193. Petersen BH, Lee TJ, Snyderman R, et al. *Neisseria meningitidis* and *Neisseria gonorrhoeae* bacteremia associated with C6, C7, or C8 deficiency. *Ann Intern Med*. 1979;90:917–920.
194. Benavent Núñez D, Tornero Marín C, Bonilla Hernán G, et al. Gonococcal arthritis and C2 deficiency. *Reumatol Clin*. 2017;pii:S1699-258X(17)30234-6.
195. Davido B, Dinh A, Lagrange A, et al. Chronic gonococcal arthritis with C5 deficiency presenting with brief flare-ups: case study and literature review. *Clin Rheumatol*. 2014;33:1351–1353.
196. Wise CM, Morris CR, Wasilauskas BL, et al. Gonococcal arthritis in an era of increasing penicillin resistance. Presentations and outcomes in 41 recent cases (1985-1991). *Arch Intern Med*. 1994;154:2690–2695.
197. Crew PE, Abara WE, McCulley L, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. *Clin Infect Dis*. 2018 [Epub ahead of print].
198. Blake M, Swanson J. Studies on *Gonococcus* infection, IX. In vitro decreased association of pilated gonococci with mouse peritoneal macrophages. *Infect Immun*. 1975;11:1402–1404.
199. Ram S, Mackinnon FG, Gulati S, et al. The contrasting mechanisms of serum resistance of *Neisseria gonorrhoeae* and group B *Neisseria meningitidis*. *Mol Immunol*. 1999;36:915–928.
200. Vogel U, Frosch M. Mechanisms of neisserial serum resistance. *Mol Microbiol*. 1999;32:1133–1139.
201. Faulstich M, Böttcher JP, Meyer TF, et al. Pilus phase variation switches gonococcal adherence to invasion by caveolin-1-dependent host cell signaling. *PLoS Pathog*. 2013;9:e1003373.
202. Stein DC, LeVan A, Hardy B, et al. Expression of opacity proteins interferes with the transmigration of *Neisseria gonorrhoeae* across polarized epithelial cells. *PLoS ONE*. 2015;10:e0134342.
203. Lewis LA, Choudhury B, Balthazar JT, et al. Phosphoethanolamine substitution of lipid A and resistance of *Neisseria gonorrhoeae* to cationic antimicrobial peptides and complement-mediated killing by normal human serum. *Infect Immun*. 2009;77:1112–1120.
204. Wang SA, Harvey AB, Conner SM, et al. Antimicrobial resistance for *Neisseria gonorrhoeae* in the United States, 1988 to 2003: the spread of fluoroquinolone resistance. *Ann Intern Med*. 2007;147:81–88.
205. Centers for Disease Control and Prevention. Gonorrhea Isolate Surveillance Project (GISP). http://www.cdc.gov/std/gisp/default.htm. Accessed June 3, 2013.
206. Workowski KA, Berman SM. Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines. *Clin Infect Dis*. 2011;53(suppl 3):S59–S63.
207. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2007;56:332–336.
208. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61:590–594.
209. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *N Engl J Med*. 2012;366:485–487.
210. Kirkcaldy RD, Bolan GA, Wasserheit JN. Cephalosporin-resistant gonorrhea in North America. *JAMA*. 2013;309:185–187.
211. Scopelitis E, Martinez-Osuna P. Gonococcal arthritis. *Rheum Dis Clin North Am*. 1993;19:363–377.
212. Brogadir SP, Schimmer BM, Myers AR. Spectrum of the gonococcal arthritis-dermatitis syndrome. *Semin Arthritis Rheum*. 1979;8:177–183.
213. Li F, Bulbul R, Schumacher HR Jr, et al. Molecular detection of bacterial DNA in venereal-associated arthritis. *Arthritis Rheum*. 1996;39:950–958.
214. Muralidhar B, Rumore PM, Steinman CR. Use of the polymerase chain reaction to study arthritis due to *Neisseria gonorrhoeae*. *Arthritis Rheum*. 1994;37:710–717.
215. Liebling MR, Arkfeld DG, Michelini GA, et al. Identification of *Neisseria gonorrhoeae* in synovial fluid using the polymerase chain reaction. *Arthritis Rheum*. 1994;37:702–709.
216. Gelfand SG, Masi AT, Garcia-Kutzbach A. Spectrum of gonococcal arthritis: evidence for sequential stages and clinical subgroups. *J Rheumatol*. 1975;2:83–90.
217. Papp JR, Schachter J, Gydos CA, et al. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* – 2014. *Morb Mortal Wkly Rpt*. 2014;63:1–19.
218. Van Der Pol B, Ferrero DV, Buck-Barrington L, et al. Multicenter evaluation of the BDProbeTec ET System for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens, female endocervical swabs, and male urethral swabs. *J Clin Microbiol*. 2001;39:1008–1016.
219. Gaydos CA, Quinn TC, Willis D, et al. Performance of the APTIMA Combo 2 assay for the multiplex detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in female urine and endocervical swab specimens. *J Clin Microbiol*. 2003;41:304–309.
220. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD. 2017.
221. Miller AC, Polgreen PM. Many opportunities to record, diagnose, or treat injection drug-related infections are missed: a population-based cohort study of inpatient and emergency department settings. *Clin Infect Dis*. 2018 Sep 11, [Epub ahead of print].
222. Oh DHW, Wurcel AG, Tybor DJ, et al. Increased mortality and reoperation rates after treatment for septic arthritis of the knee in people who inject drugs: nationwide inpatient sample, 2000-2013. *Clin Orthop Relat Res*. 2018;476:1557–1565.
223. Gordon RJ, Lowy FD. Bacterial infections in drug users. *N Engl J Med*. 2005;353:1945–1954.
224. Allison DC, Holtom PD, Patzakis MJ, et al. Microbiology of bone and joint infections in injecting drug abusers. *Clin Orthop Relat Res*. 2010;468:2107–2112.
225. Peterson TC, Pearson C2, Zekaj M, et al. Septic arthritis in intravenous drug abusers: a historical comparison of habits and pathogens. *J Emerg Med*. 2014;47:723–728.
226. Brancós MA1, Peris P, Miró JM, et al. Septic arthritis in heroin addicts. *Semin Arthritis Rheum*. 1991;21:81–87.
227. Coakley G, Mathews C, Field M, et al. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. *Rheumatology (Oxford)*. 2006;45:1039–1041.
228. Section J, Gibbons SD, Barton T, et al. Microbiological culture methods for pediatric musculoskeletal infection: a guideline for optimal use. *J Bone Joint Surg Am*. 2015;97:441–449.
229. Lee CH, Chen YJ, Ueng SW, et al. Septic arthritis of the ankle joint. *Chang Gung Med J*. 2000;23:420–426.
230. Yu KH, Luo SF, Liou LB, et al. Concomitant septic and gouty arthritis—an analysis of 30 cases. *Rheumatology (Oxford)*. 2003;42:1062–1066.
231. Colaco C, Dotel R. Coexisting polyarticular septic arthritis, gout and pseudogout. *BMJ Case Rep*. 2018;2018:pii:bcr-2018-226810.
232. Weng CT, Liu MF, Lin LH, et al. Rare coexistence of gouty and septic arthritis: a report of 14 cases. *Clin Exp Rheumatol*. 2009;27:902–906.
233. Shah K, Spear J, Nathanson LA, et al. Does the presence of crystal arthritis rule out septic arthritis? *J Emerg Med*. 2007;32:23–26.
234. Schmitt SK. Reactive arthritis. *Infect Dis Clin North Am*. 2017;31:265–277.

235. Donatto KC. Orthopedic management of septic arthritis. *Rheum Dis Clin North Am*. 1998;24:275–286.
236. Sammer DM, Shin AY. Comparison of arthroscopic and open treatment of septic arthritis of the wrist. Surgical technique. *J Bone Joint Surg Am*. 2010;92(suppl 1 Pt 1):107–113.
237. Johns BP, Loewenthal MR, Dewar DC. Open compared with arthroscopic treatment of acute septic arthritis of the native knee. *J Bone Joint Surg Am*. 2017;99:499–505.
238. Bovonratwet P, Nelson SJ, Bellamkonda K, et al. Similar 30-day complications for septic knee arthritis treated with arthrotomy or arthroscopy: an American College of Surgeons National Surgical Quality Improvement Program Analysis. *Arthroscopy*. 2018;34:213–219.
239. Stutz G, Kuster MS, Kleinstuck F, et al. Arthroscopic management of septic arthritis: stages of infection and results. *Knee Surg Sports Traumatol Arthrosc*. 2000;8:270–274.
240. de Sa D, Cargnelli S, Catapano M, et al. Efficacy of hip arthroscopy for the management of septic arthritis: a systematic review. *Arthroscopy*. 2015;31:1358–1370.
241. Dave OH, Patel KA, Andersen CR, et al. Surgical procedures needed to eradicate infection in knee septic arthritis. *Orthopedics*. 2016;39:50–54.
242. Kuo CL, Chang JH, Wu CC, et al. Treatment of septic knee arthritis: comparison of arthroscopic debridement alone or combined with continuous closed irrigation-suction system. *J Trauma*. 2011;71:454–459.
243. Memon M, Kay J, Ginsberg L, et al. Arthroscopic management of septic arthritis of the native shoulder joint. *Arthroscopy*. 2018;34:625–646.
244. Mankovecky MR, Roukis TS. Arthroscopic synovectomy, irrigation, and debridement for treatment of septic ankle arthrosis: a systematic review and case series. *J Foot Ankle Surg*. 2014;53:615–619.
245. Aim F, Delambre J, Bauer T, et al. Efficacy of arthroscopic treatment for resolving infection in septic arthritis of native joints. *Orthop Traumatol Surg Res*. 2015;101:61–64.
246. Hunter JG, Gross JM, Dahl JD, et al. Risk factors for failure of a single surgical debridement in adults with acute septic arthritis. *J Bone Joint Surg Am*. 2015;97:558–564.
247. Daynes J, Roth MF, Zekaj M, et al. Adult native septic arthritis in an inner city hospital: effects on length of stay. *Orthopedics*. 2016;39:e674–e679.
248. Stengel D, Bauwens K, Sehouli J, et al. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. *Lancet Infect Dis*. 2001;1:175–188.
249. Wieland BW, Marcantoni JR, Bommarito KM, et al. A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin-susceptible *Staphylococcus aureus*. *Clin Infect Dis*. 2012;54:585–590.
250. Winans SA, Luce AM, Hasbun R. Outpatient parenteral antimicrobial therapy for the treatment of methicillin-susceptible *Staphylococcus aureus:* a comparison of cefazolin and ceftriaxone. *Infection*. 2013;41:769–774.
251. Neely MN, Kato L, Youn G, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62:1–12.
252. Hermsen ED, Mendez-Vigo L, Berbari EF, et al. A retrospective study of outcomes of device-associated osteomyelitis treated with daptomycin. *BMC Infect Dis*. 2016;16:310–313.
253. Malizos K, Sarma J, Seaton RA, et al. Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry. *Eur J Clin Microbiol Infect Dis*. 2016;35:111–118.
254. Forrest GN, Donovan BJ, Lamp KC, et al. Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother*. 2008;42:213–217.
255. Lalani T, Boucher HW, Cosgrove SE, et al. Outcomes with daptomycin versus standard therapy for osteoarticular infections associated with *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2008;61:177–182.
256. Liang SY, Khair HN, McDonald JR, et al. Daptomycin versus vancomycin for osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA): a nested case-control study. *Eur J Clin Microbiol Infect Dis*. 2014;33:659–664.
257. Byren I, Rege S, Campanaro E, et al. Randomized controlled trial of the safety and efficacy of daptomycin versus standard-of-care therapy for management of patients with osteomyelitis associated with prosthetic devices undergoing two-stage revision arthroplasty. *Antimicrob Agents Chemother*. 2012;56:5626–5632.
258. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.
259. Roux S, Valour F, Karsenty J, et al. Daptomycin > 6 mg/kg/day as salvage therapy in patients with complex bone and joint infection: cohort study in a regional reference center. *BMC Infect Dis*. 2016;16:83.
260. Chang YJ, Lee MS, Lee CH, et al. Daptomycin treatment in patients with resistant staphylococcal periprosthetic joint infection. *BMC Infect Dis*. 2017;17:736.
261. Schrank GM, Wright SB, Branch-Elliman W, et al. A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy. *Infect Control Hosp Epidemiol*. 2018;39:947–954.
262. Bassetti M, Vitale F, Melica G, et al. Linezolid in the treatment of gram-positive prosthetic joint infections. *J Antimicrob Chemother*. 2005;55:387–390.
263. Gould FK. Linezolid: safety and efficacy in special populations. *J Antimicrob Chemother*. 2011;66(suppl 4):3–6.
264. Samuel JR, Gould FK. Prosthetic joint infections: single versus combination therapy. *J Antimicrob Chemother*. 2010;65:18–23.
265. Chen CJ, Chiu CH, Lin TY, et al. Experience with linezolid therapy in children with osteoarticular infections. *Pediatr Infect Dis J*. 2007;26:985–988.
266. Falagas ME, Siempos II, Papagelopoulos PJ, et al. Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents*. 2007;29:233–239.
267. Soriano A, Gomez J, Gomez L, et al. Efficacy and tolerability of prolonged linezolid therapy in the treatment of orthopedic implant infections. *Eur J Clin Microbiol Infect Dis*. 2007;26:353–356.
268. Morata L, Tornero E, Martínez-Pastor JC, et al. Clinical experience with linezolid for the treatment of orthopaedic implant infections. *J Antimicrob Chemother*. 2014;69:s47–s52.
269. Pfaller MA, Flamm RK, Castanheira M, et al. Dalbavancin in-vitro activity obtained against Gram-positive clinical isolates causing bone and joint infections in US and European hospitals (2011-2016). *Int J Antimicrob Agents*. 2018;51:608–611.
270. Dunne MW, Puttagunta S, Sprenger CR, et al. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother*. 2015;59:1849–1855.
271. Bouza E, Valerio M, Soriano A, et al. Dalbavancin in the treatment of different gram-positive infections: a real-life experience. *Int J Antimicrob Agents*. 2018;51:571–577.
272. Ramírez Hidalgo M, Jover-Sáenz A, García-González M, et al. Dalbavancin treatment of prosthetic knee infection due to oxacillin-resistant *Staphylococcus epidermidis*. *Enferm Infecc Microbiol Clin*. 2018;36:142–143.
273. Malandain D, Dinh A, Ferry T, et al. Salvage therapy for complex bone and joint infections with ceftaroline: a multicentre, observational study. *Int J Antimicrob Agents*. 2017;50:277–280.
274. Moenster RP, Linneman TW, Call WB, et al. The potential role of newer gram-positive antibiotics in the setting of osteomyelitis of adults. *J Clin Pharm Ther*. 2013;38:89–96.
275. Sakoulas G, Moise-Broder PA, Schentag J, et al. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004;42:2398–2402.
276. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis*. 2013;56:1562–1569.
277. Workowski KA, Bolan G. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR–3):1–138.
278. Uckay I, Tovmirzaeva L, Garbino J, et al. Short parenteral antibiotic treatment for adult septic arthritis after successful drainage. *Int J Infect Dis*. 2013;17:e199–e205.
279. Meier R, Wirth T, Hahn F, et al. Pyogenic arthritis of the fingers and the wrist: can we shorten antimicrobial treatment duration? *Open Forum Infect Dis*. 2017;4:ofx058.
280. Odio CM, Ramirez T, Arias G, et al. Double blind, randomized, placebo-controlled study of dexamethasone therapy for hematogenous septic arthritis in children. *Pediatr Infect Dis J*. 2003;22:883–888.
281. Fogel I, Amir J, Bar-On E, et al. Dexamethasone therapy for septic arthritis in children. *Pediatrics*. 2015;136:e776–e782.
282. Qin YF, Li ZJ, Li H. Corticosteroids as adjunctive therapy with antibiotics in the treatment of children with septic arthritis: a meta-analysis. *Drug Des Devel Ther*. 2018;12:2277–2284.
283. Farrow L. A systematic review and meta-analysis regarding the use of corticosteroids in septic arthritis. *BMC Musculoskelet Disord*. 2015;16:241.
284. Calabrese LH, Naides SJ. Viral arthritis. *Infect Dis Clin North Am*. 2005;19:963–980.
285. Franssila R, Hedman K. Infection and musculoskeletal conditions: viral causes of arthritis. *Best Pract Res Clin Rheumatol*. 2006;20:1139–1157.
286. Naides SJ. Rheumatic manifestations of parvovirus B19 infection. *Rheum Dis Clin North Am*. 1998;24:375–401.
287. Colmegna I, Alberts-Grill N. Parvovirus B19: its role in chronic arthritis. *Rheum Dis Clin North Am*. 2009;35:95–110.
288. Nocton JJ, Miller LC, Tucker LB, et al. Human parvovirus B19-associated arthritis in children. *J Pediatr*. 1993;122:186–190.
289. Corcoran A, Doyle S. Advances in the biology, diagnosis and host-pathogen interactions of parvovirus B19. *J Med Microbiol*. 2004;53(Pt 6):459–475.
290. Tello-Winniczuk N, Diaz-Jouanen E, Diaz-Borjon A. Parvovirus B19-associated arthritis: report on a community outbreak. *J Clin Rheumatol*. 2011;17:449–450.
291. Miyamoto K, Ogami M, Takahashi Y, et al. Outbreak of human parvovirus B19 in hospital workers. *J Hosp Infect*. 2000;45:238–241.
292. Habib GS, Zisman D. Unusual cluster of parvovirus arthritis. *Isr Med Assoc J*. 2002;4:314.
293. Scroggie DA, Carpenter MT, Cooper RI, et al. Parvovirus arthropathy outbreak in southwestern United States. *J Rheumatol*. 2000;27:2444–2448.
294. Torok TJ. Parvovirus B19 and human disease. *Adv Intern Med*. 1992;37:431–455.
295. Becker J, Winthrop KL. Update on rheumatic manifestations of infectious diseases. *Curr Opin Rheumatol*. 2010;22:72–77.
296. Waza K, Inoue K, Matsumura S. Symptoms associated with parvovirus B19 infection in adults: a pilot study. *Intern Med*. 2007;46:1975–1978.
297. Hokynar K, Norja P, Laitinen H, et al. Detection and differentiation of human parvovirus variants by commercial quantitative real-time PCR tests. *J Clin Microbiol*. 2004;42:2013–2019.
298. White DG, Woolf AD, Mortimer PP, et al. Human parvovirus arthropathy. *Lancet*. 1985;1:419–421.
299. Speyer I, Breedveld FC, Dijkmans BA. Human parvovirus B19 infection is not followed by inflammatory joint disease during long term follow-up. A retrospective study of 54 patients. *Clin Exp Rheumatol*. 1998;16:576–578.
300. Ogawa E, Otaguro S, Murata M, et al. Intravenous immunoglobulin therapy for severe arthritis associated with human parvovirus B19 infection. *J Infect Chemother*. 2008;14:377–382.
301. Kozireva SV, Zestkova JV, Mikazane HJ, et al. Incidence and clinical significance of parvovirus B19 infection in patients with rheumatoid arthritis. *J Rheumatol*. 2008;35:1265–1270.
302. Laine M, Luukkainen R, Toivanen A. Sindbis viruses and other alphaviruses as cause of human arthritic disease. *J Intern Med*. 2004;256:457–471.
303. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med*. 2015;372:1231–1239.
304. McFee RB. Selected mosquito-borne illnesses–chikungunya. *Dis Mon*. 2018;64:222–234.
305. Centers for Disease Control and Prevention. Chikungunya fever diagnosed among international travelers—United States, 2005-2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:1040–1042.
306. Centers for Disease Control and Prevention. Update: chikungunya fever diagnosed among international travelers—United States, 2006. *MMWR Morb Mortal Wkly Rep*. 2007;56:276–277.
307. Centers for Disease Control and Prevention. Chikungunya Geographic Distribution. https://www.cdc.gov/chikungunya/geo/index.html. Accessed November 15, 2018.
308. Simon F, Parola P, Grandadam M, et al. Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. *Medicine (Baltimore)*. 2007;86:123–137.
309. Burt FJ, Rolph MS, Rulli NE, et al. Chikungunya: a re-emerging virus. *Lancet*. 2012;379:662–671.
310. Parola P, Simon F, Oliver M. Tenosynovitis and vascular disorders associated with Chikungunya virus-related rheumatism. *Clin Infect Dis*. 2007;45:801–802.
311. Paixão ES, Rodrigues LC, Costa MDCN, et al. Chikungunya chronic disease: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2018;112:301–316.
312. Dupuis-Maguiraga L, Noret M, Brun S, et al. Chikungunya disease: infection-associated markers from the acute to the chronic phase of arbovirus-induced arthralgia. *PLoS Negl Trop Dis*. 2012;6:e1446.
313. Chow A, Her Z, Ong EK, et al. Persistent arthralgia induced by Chikungunya virus infection is associated

with interleukin-6 and granulocyte macrophage colony-stimulating factor. *J Infect Dis*. 2011;203:149–157.

314. Rosario V, Munoz-Louis R, Valdez T, et al. Chikungunya infection in the general population and in patients with rheumatoid arthritis on biological therapy. *Clin Rheumatol*. 2015;34:1285–1287.
315. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines. Summary of a report of the Institute of Medicine. *JAMA*. 1992;267:392–396.
316. Banatvala JE, Brown DW. Rubella. *Lancet*. 2004;363:1127–1137.
317. Smith CA, Petty RE, Tingle AJ. Rubella virus and arthritis. *Rheum Dis Clin North Am*. 1987;13:265–274.
318. Tingle AJ, Allen M, Petty RE, et al. Rubella-associated arthritis, I. Comparative study of joint manifestations associated with natural rubella infection and RA 27/3 rubella immunisation. *Ann Rheum Dis*. 1986;45:110–114.
319. Tingle AJ, Mitchell LA, Grace M, et al. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet*. 1997;349:1277–1281.
320. Howson CP, Katz M, Johnston RB Jr, et al. Chronic arthritis after rubella vaccination. *Clin Infect Dis*. 1992;15:307–312.
321. Vassilopoulos D, Calabrese LH. Viral hepatitis: review of arthritic complications and therapy for arthritis in the presence of active HBV/HCV. *Curr Rheumatol Rep*. 2013;15:319.
322. Inman RD. Rheumatic manifestations of hepatitis B virus infection. *Semin Arthritis Rheum*. 1982;11:406–420.
323. Zou CJ, Zhu LJ, Li YH, et al. The association between hepatitis B virus infection and disease activity, synovitis, or joint destruction in rheumatoid arthritis. *Clin Rheumatol*. 2013;32:787–795.
324. Buskila D, Shnaider A, Neumann L, et al. Musculoskeletal manifestations and autoantibody profile in 90 hepatitis C virus infected Israeli patients. *Semin Arthritis Rheum*. 1998;28:107–113.
325. Cesur S, Akin K, Kurt H. The significance of cryoglobulinemia in patients with chronic hepatitis B and C virus infection. *Hepatogastroenterology*. 2003;50:1487–1489.
326. Masuko-Hongo K, Kato T, Nishioka K. Virus-associated arthritis. *Best Pract Res Clin Rheumatol*. 2003;17:309–318.
327. Reveille JD, Williams FM. Infection and musculoskeletal conditions: rheumatologic complications of HIV infection. *Best Pract Res Clin Rheumatol*. 2006;20:1159–1179.
328. Mody GM, Parke FA, Reveille JD. Articular manifestations of human immunodeficiency virus infection. *Best Pract Res Clin Rheumatol*. 2003;17:265–287.
329. Nishioka K, Nakajima T, Hasunuma T, et al. Rheumatic manifestation of human leukemia virus infection. *Rheum Dis Clin North Am*. 1993;19:489–503.
330. Amissah-Arthur MB, Poller B, Tunbridge A, et al. Musculoskeletal manifestations of Ebola virus. *Rheumatology (Oxford)*. 2018;57:28–31.
331. Vetter P, Kaiser L, Schibler M, et al. Sequelae of Ebola virus disease: the emergency within the emergency. *Lancet Infect Dis*. 2016;16:e82–e91.
332. Reginato AJ. Syphilitic arthritis and osteitis. *Rheum Dis Clin North Am*. 1993;19:379–398.
333. Chaussade H, Lebeaux D, Gras G, et al. *Nocardia* arthritis: 3 cases and literature review. *Medicine (Baltimore)*. 2015;94:e1671.
334. McGill PE. Geographically specific infections and arthritis, including rheumatic syndromes associated with certain fungi and parasites, *Brucella* species and *Mycobacterium leprae*. *Best Pract Res Clin Rheumatol*. 2003;17:289–307.
335. Henry MW, Miller AO, Walsh TJ, et al. Fungal musculoskeletal infections. *Infect Dis Clin North Am*. 2017;31:353–368.
336. Bariteau JT, Waryasz GR, McDonnell M, et al. Fungal osteomyelitis and septic arthritis. *J Am Acad Orthop Surg*. 2014;22:390–401.
337. Cuellar ML, Silveira LH, Citera G, et al. Other fungal arthritides. *Rheum Dis Clin North Am*. 1993;19:439–455.
338. Ordonez ME, Farraye FA, Di Palma JA. Endemic fungal infections in inflammatory bowel disease associated with anti-TNF antibody therapy. *Inflamm Bowel Dis*. 2013;19:2490–2500.
339. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-alpha inhibitor therapy. *Drugs*. 2009;69:1403–1415.
340. Hospenthal D, Bennett J. Miscellaneous fungi and *Prototheca*. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia: Churchill Livingstone; 2000:2772–2780.
341. Dellestable F, Kures L, Mainard D, et al. Fungal arthritis due to *Pseudallescheria boydii (Scedosporium apiospermum)*. *J Rheumatol*. 1994;21:766–768.
342. Trofa D, Gacser A, Nosanchuk JD. *Candida parapsilosis,* an emerging fungal pathogen. *Clin Microbiol Rev*. 2008;21:606–625.
343. Silveira LH, Cuellar ML, Citera G, et al. *Candida* arthritis. *Rheum Dis Clin North Am*. 1993;19:427–437.
344. Gamaletsou MN, Rammaert B, Bueno MA, et al. *Candida* arthritis: analysis of 112 pediatric and adult cases. *Open Forum Infect Dis*. 2015;3:ofv207.
345. Kathresal A, Biundo J, Blais CM, et al. A rare case of *Candida* arthritis in a hemodialysis patient. *Am J Med Sci*. 2008;336:437–440.
346. Cuende E, Barbadillo C, Mazzucchelli R, et al. *Candida* arthritis in adult patients who are not intravenous drug addicts: report of three cases and review of the literature. *Semin Arthritis Rheum*. 1993;22:224–241.
347. Weems JJ Jr. *Candida parapsilosis:* epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. *Clin Infect Dis*. 1992;14:756–766.
348. Zmierczak H, Goemaere S, Mielants H, et al. *Candida glabrata* arthritis: case report and review of the literature of *Candida* arthritis. *Clin Rheumatol*. 1999;18:406–409.
349. Bariola JR, Saccente M. *Candida lusitaniae* septic arthritis: case report and review of the literature. *Diagn Microbiol Infect Dis*. 2008;61:61–63.
350. Lu H, Marengo MF, Mihu CN, et al. Rare case of septic arthritis caused by *Candida krusei:* case report and literature review. *J Rheumatol*. 2012;39:1308–1309.
351. Larru B, Barrett DM, Gerber JS. *Candida krusei* arthritis in an adolescent with acute myelogenous leukemia. *Pediatr Infect Dis J*. 2013;32:1142–1144.
352. Bisbe J, Miro JM, Latorre X, et al. Disseminated candidiasis in addicts who use brown heroin: report of 83 cases and review. *Clin Infect Dis*. 1992;15:910–918.
353. Italiano A, Yen BC, Rosenthal SA, et al. Cryptococcal osteomyelitis with septic arthritis. *Orthopedics*. 2001;24:59–60.
354. Stead KJ, Klugman KP, Painter ML, et al. Septic arthritis due to *Cryptococcus neoformans*. *J Infect*. 1988;17:139–145.
355. Zhou HX1, Lu L1, Chu T, et al. Skeletal cryptococcosis from 1977-2013. *Front Microbiol*. 2015;5:740.
356. Geller DS, Pope JB, Thornhill BA, et al. Cryptococcal pyarthrosis and sarcoidosis. *Skeletal Radiol*. 2009;38:721–727.
357. Crum NF, Lederman ER, Stafford CM, et al. Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and current controversies. *Medicine (Baltimore)*. 2004;83:149–175.
358. Galgiani J. *Coccidioides immitis*. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Churchill Livingstone; 2015:2974–2984.
359. Kushwaha VP, Shaw BA, Gerardi JA, et al. Musculoskeletal coccidioidomycosis. A review of 25 cases. *Clin Orthop*. 1996;190–199.
360. Bayer AS, Guze LB. Fungal arthritis, II. Coccidioidal synovitis: clinical, diagnostic, therapeutic, and prognostic considerations. *Semin Arthritis Rheum*. 1979;8:200–211.
361. Ong AT, Mahajan H, Chen SC, et al. Coccidioidal septic arthritis: lessons learned from a clinical and laboratory perspective. *Med J Aust*. 2012;196:705–706.
362. Saubolle MA. Laboratory aspects in the diagnosis of coccidioidomycosis. *Ann N Y Acad Sci*. 2007;1111:301–314.
363. Saubolle MA, McKellar PP, Sussland D. Epidemiologic, clinical, and diagnostic aspects of coccidioidomycosis. *J Clin Microbiol*. 2007;45:26–30.
364. MacDonald PB, Black GB, MacKenzie R. Orthopaedic manifestations of blastomycosis. *J Bone Joint Surg Am*. 1990;72:860–864.
365. Oppenheimer M, Embil JM, Black B, et al. Blastomycosis of bones and joints. *South Med J*. 2007;100:570–578.
366. Head AJ, Myers LK, Thompson JD, et al. Disseminated blastomycosis presenting as oligoarticular septic arthritis in a 12-year-old girl. *Arthritis Rheum*. 2005;53:138–141.
367. Bayer AS, Scott VJ, Guze LB. Fungal arthritis, IV. Blastomycotic arthritis. *Semin Arthritis Rheum*. 1979;9:145–151.
368. George AL Jr, Hays JT, Graham BS. Blastomycosis presenting as monoarticular arthritis. The role of synovial fluid cytology. *Arthritis Rheum*. 1985;28:516–521.
369. Darouiche RO, Cadle RM, Zenon GJ, et al. Articular histoplasmosis. *J Rheumatol*. 1992;19:1991–1993.
370. Fowler VG Jr, Nacinovich FM, Alspaugh JA, et al. Prosthetic joint infection due to *Histoplasma capsulatum:* case report and review. *Clin Infect Dis*. 1998;26:1017.
371. Friedman SJ, Black JL, Duffy J. Histoplasmosis presenting as erythema multiforme and polyarthritis. *Cutis*. 1984;34:396–398.
372. Rosenthal J, Brandt KD, Wheat LJ, et al. Rheumatologic manifestations of histoplasmosis in the recent Indianapolis epidemic. *Arthritis Rheum*. 1983;26:1065–1070.
373. Vismer HF, Hull PR. Prevalence, epidemiology and geographical distribution of *Sporothrix schenckii* infections in Gauteng, South Africa. *Mycopathologia*. 1997;137:137–143.
374. Gottlieb GS, Lesser CF, Holmes KK, et al. Disseminated sporotrichosis associated with treatment with immunosuppressants and tumor necrosis factor-alpha antagonists. *Clin Infect Dis*. 2003;37:838–840.
375. Heller HM, Fuhrer J. Disseminated sporotrichosis in patients with AIDS: case report and review of the literature. *AIDS*. 1991;5:1243–1246.
376. Howell SJ, Toohey JS. Sporotrichal arthritis in south central Kansas. *Clin Orthop*. 1998;207–214.
377. Bayer AS, Scott VJ, Guze LB. Fungal arthritis, III. Sporotrichal arthritis. *Semin Arthritis Rheum*. 1979;9:66–74.
378. Chowdhary G, Weinstein A, Klein R, et al. Sporotrichal arthritis. *Ann Rheum Dis*. 1991;50:112–114.
379. Jones N. Photo quiz. Osteoarticular sporotrichosis. *Clin Infect Dis*. 1999;29:59, 202–259, 203.
380. Crout JE, Brewer NS, Tompkins RB. Sporotrichosis arthritis: clinical features in seven patients. *Ann Intern Med*. 1977;86:294–297.
381. Golmia R, Bello I, Marra A, et al. *Aspergillus fumigatus* joint infection: a review. *Semin Arthritis Rheum*. 2011;40:580–584.

381a. Gamaletsou MN, Rammaert B, Bueno MA, et al. *Aspergillus* arthritis: analysis of clinical manifestations, diagnosis, and treatment of 31 reported cases. *Med Mycol*. 2017;55:246–254.

382. Brandt ME, Warnock DW. Epidemiology, clinical manifestations, and therapy of infections caused by dematiaceous fungi. *J Chemother*. 2003;15(suppl 2):36–47.
383. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev*. 2008;21:157–197.
384. Charles JF, Eberle C, Daikh DI, et al. Resolution of recurrent *Fusarium* arthritis after prolonged antifungal therapy. *J Clin Rheumatol*. 2011;17:44–45.
385. Kumashi PR, Safdar A, Chamilos G, et al. Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: a 10-year retrospective review. *Clin Microbiol Infect*. 2006;12:621–626.
386. McWhinney PH, Madgwick JC, Hoffbrand AV, et al. Successful surgical management of septic arthritis due to *Trichosporon beigelii* in a patient with acute myeloid leukaemia. *Scand J Infect Dis*. 1992;24:245–247.
387. Taj-Aldeen SJ, Gamaletsou MN, Rammaert B, et al. Bone and joint infections caused by mucormycetes: a challenging osteoarticular mycosis of the twenty-first century. *Med Mycol*. 2017;55:691–704.
388. Taj-Aldeen SJ, Rammaert B, Gamaletsou M, et al. Osteoarticular infections caused by non-*Aspergillus* filamentous fungi in adult and pediatric patients: a systematic review. *Medicine (Baltimore)*. 2015;94:e2078.
389. Muscolo DL, Carbo L, Aponte-Tinao LA, et al. Massive bone loss from fungal infection after anterior cruciate ligament arthroscopic reconstruction. *Clin Orthop Relat Res*. 2009;467:2420–2425.
390. Sun L, Zhang L, Wang K, et al. Fungal osteomyelitis after arthroscopic anterior cruciate ligament reconstruction: a case report with review of the literature. *Knee*. 2012;19:728–731.
391. Sohail MR, Smilack JD. *Aspergillus fumigatus* septic arthritis complicating intra-articular corticosteroid injection. *Mayo Clin Proc*. 2004;79:578–579.
392. Centers for Disease Control and Prevention. Multi-state Meningitis Outbreak—Current Case Count. Persons With Fungal Infections Linked to Steroid Injections, by State; May 6, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html. Accessed June 3, 2013.
393. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291–322.
394. Kauffman CA, Bustamante B, Chapman SW, et al. Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:1255–1265.
395. Lewis RE. Current concepts in antifungal pharmacology. *Mayo Clin Proc*. 2011;86:805–817.
396. Lass-Florl C. Triazole antifungal agents in invasive fungal infections: a comparative review. *Drugs*. 2011;71:2405–2419.
397. Zonios DI, Bennett JE. Update on azole antifungals. *Semin Respir Crit Care Med*. 2008;29:198–210.
398. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs*. 2011;71:11–41.
399. Revankar SG, Baddley JW, Chen SC, et al. A Mycoses Study Group international prospective study of

phaeohyphomycosis: an analysis of 99 proven/probable cases. *Open Forum Infect Dis*. 2017;4:ofx200.

400. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;61:1558–1565.
401. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–e50.
402. Pfaller MA, Messer SA, Woosley LN, et al. Echinocandin and triazole antifungal susceptibility profiles of opportunistic yeast and mould clinical isolates (2010-2011): application of new CLSI clinical breakpoints and epidemiological cutoff values to characterize geographic and temporal trends of antifungal resistance. *J Clin Microbiol*. 2013;51:2571–2581.
403. Sili U, Yilmaz M, Ferhanoglu B, et al. *Candida krusei* arthritis in a patient with hematologic malignancy: successful treatment with voriconazole. *Clin Infect Dis*. 2007;45:897–898.
404. Beyda ND, Lewis RE, Garey KW. Echinocandin resistance in *Candida* species: mechanisms of reduced susceptibility and therapeutic approaches. *Ann Pharmacother*. 2012;46:1086–1096.
405. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46:1801–1812.
406. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63:e112–e146.
407. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–825.
408. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1–e60.
409. Howard SJ, Cerar D, Anderson MJ, et al. Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure. *Emerg Infect Dis*. 2009;15:1068–1076.
410. Centers for Disease Control and Prevention. Interim Treatment Guidance for Osteoarticular Infections Associated With Injection of Contaminated Steroid Products; October 23, 2012. http://www.cdc.gov/hai/outbreaks/clinicians/treatment-joints.html. Accessed June 3, 2013.
411. Malaviya AN, Kotwal PP. Arthritis associated with tuberculosis. *Best Pract Res Clin Rheumatol*. 2003;17:319–343.
412. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis*. 2004;39:295–299.
413. Hogan JI, Hurtado RM, Nelson SB. Mycobacterial musculoskeletal infections. *Infect Dis Clin North Am*. 2017;31:369–382.
414. Eder L, Zisman D, Rozenbaum M, et al. Clinical features and aetiology of septic arthritis in northern Israel. *Rheumatology (Oxford)*. 2005;44:1559–1563.
415. Yang Z, Kong Y, Wilson F, et al. Identification of risk factors for extrapulmonary tuberculosis. *Clin Infect Dis*. 2004;38:199–205.
416. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
417. Huang TY, Wu TS, Yang CC, et al. Tuberculous arthritis—a fourteen-year experience at a tertiary teaching hospital in Taiwan. *J Microbiol Immunol Infect*. 2007;40:493–499.
418. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of "difficult" multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2008;12:345–346.
419. Suarez-Garcia I, Noguerado A. Drug treatment of multidrug-resistant osteoarticular tuberculosis: a systematic literature review. *Int J Infect Dis*. 2012;16:e774–e778.
420. Garrido G, Gomez-Reino JJ, Fernandez-Dapica P, et al. A review of peripheral tuberculous arthritis. *Semin Arthritis Rheum*. 1988;18:142–149.
421. Klofkorn RW, Steigerwald JC. Carpal tunnel syndrome as the initial manifestation of tuberculosis. *Am J Med*. 1976;60:583–586.
422. Kramer N, Rosenstein ED. Rheumatologic manifestations of tuberculosis. *Bull Rheum Dis*. 1997;46:5–8.
423. Sun YS, Lou SQ, Wen JM, et al. Clinical value of polymerase chain reaction in the diagnosis of joint tuberculosis by detecting the DNA of *Mycobacterium tuberculosis*. *Orthop Surg*. 2011;3:64–71.
424. Sun YS, Wen JM, Lu WX, et al. Comparison study on polymerase chain reaction (PCR) and standard culture technique in detecting *Mycobacterium tuberculosis* to diagnose joint tuberculosis. *Zhongguo Gu Shang*. 2009;22:504–506, [in Chinese].
425. Fujimoto N, Gemba K, Yao A, et al. Tuberculosis diagnosed by PCR analysis of synovial fluid. *J Infect Chemother*. 2010;16:53–55.
426. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:e1–e33.
427. Choi JA, Koh SH, Hong SH, et al. Rheumatoid arthritis and tuberculous arthritis: differentiating MRI features. *AJR Am J Roentgenol*. 2009;193:1347–1353.
428. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
429. Deleted in review.
430. Hsiao CH, Cheng A, Huang YT, et al. Clinical and pathological characteristics of mycobacterial tenosynovitis and arthritis. *Infection*. 2013;41:457–464.
431. Kozin SH, Bishop AT. Atypical *Mycobacterium* infections of the upper extremity. *J Hand Surg Am*. 1994;19:480–487.
432. Riera J, Conesa X, Pisa J, et al. Septic arthritis caused by *Mycobacterium marinum*. *Arch Orthop Trauma Surg*. 2016;136:131–134.
433. Salliot C, Desplaces N, Boisrenoult P, et al. Arthritis due to *Mycobacterium xenopi*: a retrospective study of 7 cases in France. *Clin Infect Dis*. 2006;43:987–993.
434. Ip FK, Chow SP. *Mycobacterium fortuitum* infections of the hand. Report of five cases. *J Hand Surg [Br]*. 1992;17:675–677.
435. Wallace RJ Jr, Brown BA, Onyi GO. Skin, soft tissue, and bone infections due to *Mycobacterium chelonae chelonae:* importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. *J Infect Dis*. 1992;166:405–412.
436. Khermosh O, Weintroub S, Topilsky M, et al. *Mycobacterium abscessus (M. chelonae)* infection of the knee joint: report of two cases following intra-articular injection of corticosteroids. *Clin Orthop*. 1979;162–168.
437. Fukui S, Sekiya N, Takizawa Y, et al. Disseminated *Mycobacterium abscessus* infection following septic arthritis. *Medicine (Baltimore)*. 2015;94:e861.
438. Salvana EM, Cooper GS, Salata RA. *Mycobacterium* other than tuberculosis (MOTT) infection: an emerging disease in infliximab-treated patients. *J Infect*. 2007;55:484–487.
439. Jousse-Joulin S, Garre M, Guennoc X, et al. Skin and joint infection by *Mycobacterium chelonae:* rescue treatment with interferon gamma. *Joint Bone Spine*. 2007;74:385–388.
440. Loddenkemper K, Enzweiler C, Loddenkemper C, et al. Granulomatous synovialitis with erosions in the shoulder joint: a rare case of polyarthritis caused by *Mycobacterium kansasii*. *Ann Rheum Dis*. 2005;64:1088–1090.
441. Meier JL, Beekmann SE. Mycobacterial and fungal infections of bone and joints. *Curr Opin Rheumatol*. 1995;7:329–336.
442. van Ingen J. Diagnosis of nontuberculous mycobacterial infections. *Semin Respir Crit Care Med*. 2013;34:103–109.
443. Zenone T, Boibieux A, Tigaud S, et al. Non-tuberculous mycobacterial tenosynovitis: a review. *Scand J Infect Dis*. 1999;31:221–228.
444. Harth M, Ralph ED, Faraawi R. Septic arthritis due to *Mycobacterium marinum*. *J Rheumatol*. 1994;21:957–960.
445. Small LN, Ross JJ. Suppurative tenosynovitis and septic bursitis. *Infect Dis Clin North Am*. 2005;19:991–1005.
446. Baumbach SF, Lobo CM, Badyine I, et al. Prepatellar and olecranon bursitis: literature review and development of a treatment algorithm. *Arch Orthop Trauma Surg*. 2014;134:359–370.
447. Reilly D, Kamineni S. Olecranon bursitis. *J Shoulder Elbow Surg*. 2016;25:158–167.
448. Canoso JJ, Barza M. Soft tissue infections. *Rheum Dis Clin North Am*. 1993;19:293–309.
449. Weinstein PS, Canoso JJ, Wohlgethan JR. Long-term follow-up of corticosteroid injection for traumatic olecranon bursitis. *Ann Rheum Dis*. 1984;43:44–46.
450. Skedros JG, Keenan KE, Trachtenberg JD. *Candida glabrata* olecranon bursitis treated with bursectomy and intravenous caspofungin. *J Surg Orthop Adv*. 2013;22:179–182.
451. Mathew SD, Tully CC, Borra H, et al. Septic subacromial bursitis caused by *Mycobacterium kansasii* in an immunocompromised host. *Mil Med*. 2012;177:617–620.
452. de Montclos M, Chatte G, Perrin-Fayolle M, et al. Olecranon bursitis due to *Prototheca wickerhamii,* an algal opportunistic pathogen. *Eur J Clin Microbiol Infect Dis*. 1995;14:561–562.
453. Know J, Coloe S, Perera C, et al. *Prototheca wickerhamii* olecranon bursitis successfully treated with adjunctive systemic itraconazole. *Pathology*. 2015;47:388–390.
454. Aaron DL, Patel A, Kayiaros S, et al. Four common types of bursitis: diagnosis and management. *J Am Acad Orthop Surg*. 2011;19:359–367.
455. Dillon JP, Freedman I, Tan JS, et al. Endoscopic bursectomy for the treatment of septic pre-patellar bursitis: a case series. *Arch Orthop Trauma Surg*. 2012;132:921–925.
456. Abzug JM, Chen NC, Jacoby SM. Septic olecranon bursitis. *J Hand Surg Am*. 2012;37:1252–1253.
457. Sayegh ET, Strauch RJ. Treatment of olecranon bursitis: a systematic review. *Arch Orthop Trauma Surg*. 2014;134:1517–1536.

104 Osteomyelitis

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SHORT VIEW SUMMARY

CLASSIFICATION

- Osteomyelitis can develop as the result of contiguous spread from adjacent soft tissues and joints, hematogenous seeding, or direct inoculation of microorganisms into the bone as a result of trauma or surgery.
- The Cierny-Mader classification is based on the affected portion of the bone, the physiologic status of the host, and the local environment.
- The Lew and Waldvogel classification is based on the duration of illness (acute versus chronic), the mechanism of infection (hematogenous vs. contiguous), and the presence of vascular insufficiency.

GENERAL PRINCIPLES

- The diagnosis of osteomyelitis is suspected on clinical grounds. Confirmation usually entails a combination of radiologic, microbiologic, and pathologic tests.
- Cross-sectional imaging modalities, such as computed tomography or magnetic resonance imaging (MRI), are considered standard of care in the diagnosis of osteomyelitis.
- Repeated swab cultures of the same organism from draining wounds and sinus tracts may be of diagnostic benefit, although recovered organisms (except for *Staphylococcus aureus*) may not reflect the true pathogen.
- Surgical culture, bone biopsy, or needle aspiration is best for organism identification.
- Therapy is typically a combination of complete surgical débridement and 4 to 6 weeks of antimicrobial therapy (see Table 104.3).

OSTEOMYELITIS AFTER A CONTAMINATED OPEN FRACTURE

- Contaminated open fractures can lead to the development of osteomyelitis of the fractured bone, typically at the fracture site in 3% to 25% of cases.
- Staphylococci and aerobic gram-negative bacilli are the two most common groups of microorganisms in this setting.
- The hallmark of osteomyelitis after open fracture is nonunion of the fracture site or poor wound healing after wound closure or soft tissue coverage.
- Management of open contaminated fractures typically entails early aggressive wound irrigation and débridement, administration of parenteral and local antimicrobials, fracture fixation, and soft tissue coverage of exposed bone.

VERTEBRAL OSTEOMYELITIS AND SPONDYLODISKITIS

- The origin is hematogenous in most native cases; it may also occur postoperatively or postprocedurally.
- *S. aureus*, coagulase-negative staphylococci, and streptococci are the most common microorganisms encountered in pyogenic vertebral osteomyelitis.
- MRI of the spine is highly accurate in the diagnosis of vertebral osteomyelitis.
- Image-guided aspiration and biopsy is highly specific but lacks sensitivity.
- Most cases can be treated with a 6-week course of parenteral antimicrobial therapy without surgery.

OSTEOMYELITIS IN PATIENTS WITH DIABETES MELLITUS OR VASCULAR INSUFFICIENCY

- Patients typically have osteomyelitis contiguous with an ulcer of the lower extremity.
- The sensitivity of exposed bone or a probe-to-bone test was 60%, and the specificity was 91%.
- This category of osteomyelitis is often polymicrobial.
- Therapy typically requires a combination of broad-spectrum antimicrobial regimen and surgical débridement.

ACUTE HEMATOGENOUS OSTEOMYELITIS

- Acute hematogenous osteomyelitis of long bones occurs mainly in prepubertal children, intravenous drug abusers, and patients with indwelling central catheters.
- The most common recovered microorganism is *S. aureus*.
- Acute hematogenous osteomyelitis of long bones in prepubertal children is typically treated with a 2- to 3-week course of antimicrobial therapy.

CLASSIFICATION

Despite advances in surgical and medical management of osteomyelitis, it is still considered one of the most difficult-to-treat infectious diseases. Progressive destruction of the bone and the formation of sequestra are characteristics of this disease. Osteomyelitis can develop as the result of contiguous spread from adjacent soft tissues and joints, hematogenous seeding, or direct inoculation of microorganisms into the bone as a result of trauma or surgery.[1] When established, microorganisms produce a local inflammatory reaction that promotes bone necrosis and the formation of sequestra. *Staphylococcus aureus,* the most common microorganism recovered in osteomyelitis, preferentially causes this disease by expressing high-affinity adhesins to components of bone matrix that express fibronectin, laminin, collagen, or sialoglycoprotein. There are two major osteomyelitis classification schemes. Cierny and Mader[2] classified osteomyelitis based on the affected portion of the bone, the physiologic status of the host, and the local environment (Table 104.1). This classification lends itself to the treatment and prognosis of osteomyelitis. Stage 1 osteomyelitis typically can be treated with antimicrobial therapy alone, whereas stage 3 disease most often is managed with aggressive surgical débridement, antimicrobial therapy, and delayed orthopedic reconstruction. Lew and Waldvogel[3] classified osteomyelitis based on the duration of illness (acute vs. chronic), the mechanism of infection (hematogenous vs. contiguous), and the presence of vascular insufficiency. In contrast to the Cierny and Mader classification, the Waldvogel classification is an etiologic classification and does not implicate a specific therapeutic strategy.

Because of differences in pathophysiology, diagnosis, and management, long bone osteomyelitis, osteomyelitis resulting from open fractures, vertebral osteomyelitis, osteomyelitis in patients with diabetes mellitus and peripheral vascular insufficiency, acute hematogenous osteomyelitis, and SAPHO (*s*ynovitis, *a*cne, *p*lantar pustulosis, *h*yperostosis, and *o*steitis) syndrome are discussed separately. In addition, osteomyelitis in specific hosts (e.g., sickle cell disease), in unusual locations (e.g., clavicle), and secondary to unusual microorganisms are reviewed.

LESSONS FROM EXPERIMENTAL MODELS

Because of the lack of well-designed prospective clinical trials to guide the management of patients with osteomyelitis, recommendations about management of this disease have been primarily derived from

TABLE 104.1 Staging System of Osteomyelitis

Anatomic Type
Stage 1: Medullary osteomyelitis
Stage 2: Superficial osteomyelitis
Stage 3: Localized osteomyelitis
Stage 4: Diffuse osteomyelitis
Physiologic Class
A Host: Normal host
B Host: Systemic compromise (Bs)
Local compromise (Bi)
Systemic and local compromise (Bis)
C Host: Treatment worse than the disease

Systemic or Local Factors That Affect Immune Surveillance, Metabolism, and Local Vascularity

SYSTEMIC (Bs)	LOCAL (Bi)
Malnutrition	Chronic lymphedema
Renal, hepatic failure	Major vessel compromise
Diabetes mellitus	Small vessel disease
Chronic hypoxia	Vasculitis
Immune disease	Venous stasis
Malignancy	Extensive scarring
Extremes of age	Radiation fibrosis
Immunosuppression	Neuropathy
	Tobacco abuse

From Mader JT, Shirtliff M, Calhoun JH. Staging and staging application in osteomyelitis. Clin Infect Dis. *1997;25:1303–1309.*

experimental animal models, expert opinion, and retrospective cohort studies. Experimental models have been developed mainly to study the pathogenesis and treatment of osteomyelitis and offer a more controlled approach to a heterogeneous disease.[4]

Pathogenesis in Experimental Models

In experimental models, normal bone is highly resistant to infection. Osteomyelitis in this setting can be created only after inoculation of large inocula and the creation of bone necrosis, which can result from bone trauma or surgery or can be due to the presence of foreign bodies.[5,6] When digested by osteoblasts, *S. aureus* can survive in a metabolically less active and phenotypically altered state for a prolonged period of time. This small colony variant phenotype leads to impaired antimicrobial activity, particularly with antimicrobials that interfere with cell wall synthesis, and reduced production of proinflammatory molecules.[7,8] These characteristics might explain, in part, the high relapse rate of osteomyelitis treated with a short course of antimicrobials and the long incubation period.[5,6] Muller and associates[9] studied leukocyte mobilization and phagocytosis in a guinea pig model of posttraumatic osteomyelitis. In this model, leukocyte locomotion was reduced after trauma and infection with *S. aureus* for 90 days.[9]

Antimicrobial Therapy in Experimental Models

Norden and coworkers[10] analyzed the effect of the duration of antimicrobial therapy on the rate of bone sterilization in an experimental model of chronic *S. aureus* osteomyelitis that did not include surgical débridement as part of the experimental treatment. Of cultures, 78% and 16% yielded bacterial growth after 14 and 28 days of clindamycin therapy, respectively. These data support the need for a prolonged course of antimicrobial therapy in osteomyelitis. To our knowledge, the optimal duration of antimicrobial therapy after surgical débridement in an experimental model has not been studied.

Given the importance of biofilm production and the role of rifampin in killing microorganisms present in biofilms, several animal models of staphylococcal osteomyelitis have analyzed the efficacy of rifampin, alone or in combination with β-lactams, vancomycin, macrolides, and quinolones. Combinations of rifampin with other antimicrobial agents generally were more effective in sterilizing the bone.[11,12]

The effect of fluoroquinolones on the healing process of bone fractures was assessed by Huddleston and colleagues.[13] In this study, 60 rats were divided equally into three groups, each group receiving ciprofloxacin, cefazolin, or no treatment for 3 weeks. Radiographs revealed significantly impaired healing of fractures in the ciprofloxacin-treated group compared with fractures in the cefazolin-treated group. Additional studies have shown this effect with other fluoroquinolones but not with vancomycin or gentamicin.[14,15] Quinolones should be used cautiously and when other antimicrobials are not available in cases of osteomyelitis in which fracture healing needs to occur concomitantly with antimicrobial administration. Given the inherent difficulties of conducting large prospective clinical trials in humans, the management of osteomyelitis is likely to continue to be guided by lessons learned from experimental animal models.

GENERAL PRINCIPLES

Osteomyelitis can be hematogenous or contiguous to a soft tissue infection. Acute hematogenous infectious osteomyelitis in children is discussed separately. Adults usually have vague symptoms with a subacute-to-chronic presentation. Nonspecific pain around the involved site with the absence of systemic signs and symptoms is normal. Fever, chills, local swelling, and erythema in the proximity of the involved bone are seldom seen. A draining sinus tract may be present over the involved bone. It usually evolves over several months and sometimes years.

General Principles of Diagnosis

The diagnosis of osteomyelitis is first suspected on clinical grounds. Confirmation usually entails a combination of radiologic, microbiologic, and pathologic tests. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often elevated. The white blood cell count can be normal or elevated.

Although insensitive, a conventional radiograph is inexpensive and readily available. Abnormalities are usually seen 10 to 14 days after onset of the infection. Nuclear bone scans, although sensitive, are expensive and sometimes nonspecific. Technetium 99m (^{99m}Tc) methylene diphosphonate, gallium (Ga)-67 citrate, and indium (In) 111–labeled white blood cells commonly are used as tracers. Degenerative joint disease, bone tumors, and recent surgery can give false-positive results. These tests require more than 1 day for completion. Fluorine 18 (^{18}F) fluorodeoxyglucose positron emission tomography (PET) imaging is associated with a high sensitivity and specificity for the diagnosis of osteomyelitis, but is very expensive.[16] The high-resolution tomographic images, availability of the agents, and rapid completion are favorable traits of this imaging modality. Cross-sectional imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are considered standard of care in the diagnosis of osteomyelitis (Figs. 104.1 and 104.2). Although expensive, they are very sensitive. In certain circumstances, such as Charcot arthropathy, these imaging modalities lack specificity.[17,18] These modalities have an excellent anatomic delineation of the infectious process and an excellent resolution of the surrounding soft tissue. Given the high sensitivity of these tests, they are mostly used to rule out osteomyelitis.[18] Although the presence of hardware may limit the use of conventional MRI sequences, the use of metal artifact suppression techniques, such as multiacquisition variable-resonance image combination (MAVRIC), improves image quality, allowing use of MRI in this setting.[19] The presence of a cardiac device is not an absolute contraindication to MRI.

General Principles of Microbiologic Diagnosis

The identification of a causative microorganism is crucial. The type of organism and the associated in vitro susceptibility data help optimize medical therapy. Organism identification is best accomplished by means of surgical sampling or with needle aspiration under radiologic guidance to obtain tissues for histopathologic examination and aerobic and anaerobic bacterial culture. If a bacterial pathogen is not identified, less common causes of osteomyelitis should be considered and evaluation should be guided by the clinical context.

Swab cultures from draining wounds and sinus tracts can be of diagnostic benefit for three reasons. First, the identification of certain resistant microorganisms (e.g., methicillin-resistant *S. aureus* [MRSA],

FIG. 104.1 Magnetic resonance T2 axial image of the left tibia reveals abnormality of the middle and proximal portion of the tibia (white changes, *arrows*). During surgery, there was significant amount of purulence and osteomyelitis bone present. Cultures grew *Pseudomonas aeruginosa.*

FIG. 104.2 Computed tomography reconstruction images of a nonunited femur fracture 6 months after intramedullary nailing. Surgical cultures grew *Pseudomonas aeruginosa* and *Propionibacterium acnes.*

TABLE 104.2 Microbiology of Osteomyelitis

Common (>50% of Cases)
Staphylococcus aureus
Coagulase-negative staphylococci
Occasionally Encountered (<25% of Cases)
Streptococci
Enterococci
Pseudomonas spp.
Enterobacter spp.
Proteus spp.
Escherichia coli
Serratia spp.
Anaerobes (*Finegoldia [Peptostreptococcus]* spp., *Clostridium* spp., *Bacteroides fragilis* group)
Mycobacterium tuberculosis
Rarely Encountered (<5% of Cases)
Mycobacterium avium-intracellulare complex
Rapidly growing mycobacteria
Dimorphic fungi (blastomycosis, coccidioidomycosis, sporotrichosis)
Candida spp.
Cryptococcus
Aspergillus spp.
Mycoplasma spp.
Tropheryma whipplei
Brucella spp.
Salmonella spp.
Actinomyces

vancomycin-resistant enterococci) indicates the need for infection-control measures. Second, the isolation of *S. aureus* from superficial cultures has a high degree of correlation with deep cultures.[20] However, the majority of sinus tract swabs obtained during *S. aureus* osteomyelitis will not grow this organism, highlighting the lack of sensitivity of this test. The recovery of other microorganisms correlates poorly with deep cultures. Third, the recovery of the same organism on two consecutive cultures, although infrequent, has been shown to highly correlate with deep surgical cultures of bones.[21]

In hematogenous long bone osteomyelitis, the infection is usually monobacterial, whereas in contiguous infection it is usually polymicrobial. *S. aureus,* coagulase-negative staphylococci, aerobic gram-negative bacteria, and *Finegoldia* (formerly *Peptostreptococcus*) spp. are the most common organisms encountered (Table 104.2). Community-acquired MRSA (CA-MRSA) has been increasingly recognized as a cause of acute long bone osteomyelitis and diskitis in children.[22] Panton-Valentine leukocidin (PVL) is a cytotoxin found in CA-MRSA strains. In children, osteomyelitis caused by PVL-positive *S. aureus* is associated with multifocal and more aggressive disease when compared with PVL-negative *S. aureus*.[23]

General Principles of Therapy

The goal of therapy for osteomyelitis is to eradicate the infection and to restore function. Most cases of osteomyelitis in adults require a combination of medical and surgical therapy for successful eradication of the infection. It has long been recognized that antimicrobial therapy alone is not curative in most cases of osteomyelitis. In 1944, with the introduction of penicillin, Key[24] wrote: "continuous drug over a long period of time will lessen the amount of discharge, but it will not cure the disease because it cannot sterilize dead bone or cavities with necrotic content and rigid walls." All antimicrobials should be withheld if possible until percutaneous aspirate or surgical deep cultures have been obtained, unless there is concomitant soft tissue infection or sepsis syndrome. Antimicrobials are usually started (Table 104.3) immediately after surgical débridement (Table 104.4).

Established Agents for Antimicrobial Therapy

β-Lactams and vancomycin are the most commonly used antimicrobials in the medical management of osteomyelitis.[25,26] Cephalosporins are commonly used in patients with osteomyelitis because of their low toxicity profile and their spectrum of activity against staphylococci and other common bacterial pathogens that cause osteomyelitis. Cefazolin has excellent activity against methicillin-sensitive staphylococci, is safe and inexpensive, and has been used extensively in medical therapy for osteomyelitis.[25] The penicillinase-resistant penicillins have excellent antistaphylococcal activity and are commonly used, but carry a higher rate of adverse effects requiring alteration in therapy during outpatient parenteral antimicrobial therapy (OPAT), compared with cefazolin.[27,28] Ceftriaxone once daily is convenient for outpatient therapy; its use in methicillin-sensitive staphylococcal osteomyelitis has been advocated by some experts.[25,29]

Vancomycin is used commonly in the treatment of osteomyelitis because of its activity against methicillin-resistant staphylococci and

TABLE 104.3 Antimicrobial Therapy for Chronic Osteomyelitis in Adults for Selected Microorganisms

MICROORGANISMS	FIRST CHOICE[a]	ALTERNATIVE CHOICE[a]
Staphylococci		
Oxacillin sensitive	Nafcillin sodium or oxacillin sodium, 1.5–2 g IV q4–6h for 4–6 wk, *or* cefazolin,[b] 1–2 g IV q8h for 4–6 wk	Vancomycin, 15 mg/kg IV q12h for 4–6 wk; some add rifampin, 600 mg PO qd, to nafcillin/oxacillin
Oxacillin resistant (MRSA)	Vancomycin, 15 mg/kg IV q12h for 4–6 wk *or* Daptomycin 6 mg/kg IV q24h[d]	Linezolid, 600 mg PO/IV q12h for 6 wk, *or* levofloxacin,[c] 500–750 mg PO/IV daily, plus rifampin, 600–900 mg/day PO for 6 wk if susceptible to both drugs
Penicillin-sensitive streptococci	Aqueous crystalline penicillin G, 20×10^6 U/24 h IV either continuously or in 6 equally divided daily doses for 4–6 wk, or ceftriaxone, 2 g IV *or* IM q24h for 4–6 wk *or* cefazolin, 1–2 g IV q8h for 4–6 wk	Vancomycin, 15 mg/kg IV q12h for 4–6 wk
Enterococci or streptococci with MIC ≥0.5 μg/mL, *or Abiotrophia* or *Granulicatella* spp.	Aqueous crystalline penicillin G, 20×10^6 U/24 h IV either continuously or in 6 equally divided daily doses for 4–6 wk, *or* ampicillin sodium, 12 g/24 h IV either continuously or in 6 equally divided daily doses; the addition of gentamicin sulfate, 1 mg/kg IV or IM q8h for 1–2 wk is *optional*	Vancomycin, 15 mg/kg IV q12h for 4–6 wk; the addition of gentamicin sulfate, 1 mg/kg IV *or* IM q8h for 1–2 wk is *optional*
Enterobacteriaceae	Ceftriaxone, 1–2 g IV q24h for 4–6 wk, *or* ertapenem 1 g IV q24h	Ciprofloxacin,[c] 500–750 mg PO q12h for 4–6 wk, *or* levofloxacin 500–750 mg PO q24h
Pseudomonas aeruginosa	Cefepime, 2 g IV q8–12h, meropenem, 1 g IV q8h *or* imipenem, 500 mg IV q6h for 4–6 wk	Ciprofloxacin,[c] 750 mg PO q12h for 4–6 wk, *or* ceftazidime, 2 g IV q8h

[a]Antimicrobial selection should be based on in vitro sensitivity data.
[b]Use 2 g for patients weighing 80 kg or more.
[c]Should be avoided, if possible, in pediatric patients and in osteomyelitis associated with fractures.
[d]Some experts recommend use of 8–10 mg/kg IV q24h.
MIC, Minimal inhibitory concentration; *MRSA,* methicillin-resistant *Staphylococcus aureus.*

TABLE 104.4 Surgical Principles in Osteomyelitis

Adequate drainage of all infected tissue
Extensive débridement of all infected tissue
Removal of all hardware
Management of dead space (flap)
Complete wound closure
Stability of infected fracture

ampicillin-resistant enterococci. In a large cohort study of 450 patients with osteomyelitis who were followed for 10 years, vancomycin was associated with a 2.5 relative risk of recurrence, compared with a penicillinase-resistant penicillin in a univariate analysis.[25] Because of the high failure rate and the increasing minimal inhibitory concentration among many staphylococcus strains, many experts now advocate the use of higher and continuous dosage of vancomycin, keeping trough levels between 15 and 20 μg/mL.[30,31] However, the data suggesting that higher trough levels improve outcomes are lacking, and rates of acute kidney injury are increased with this strategy.[32] Linezolid and tedizolid are oxazolidinone class antimicrobials with excellent activity against staphylococci, streptococci, and vancomycin-resistant enterococci. Both agents have excellent bioavailability when administered orally. Available since 2000 in the United States, linezolid has been used in patients with infections caused by vancomycin-resistant enterococci or when β-lactams or vancomycin cannot be used.[30,33] Prolonged use of linezolid has been associated with significant pancytopenia, peripheral neuropathy, optic neuritis, and lactic acidosis.[34,35] Because of its toxicity profile and experimental models showing a high failure rate, the use of linezolid in patients with osteomyelitis typically has been limited to patients with osteomyelitis caused by vancomycin-resistant enterococci or patients who are intolerant of vancomycin.[33,36] The use of linezolid therapy guided by level may ameliorate some of the risk of chronic toxicity and drug interactions when the drug is used in combination with rifampin.[37] Available since 2014, tedizolid has not been widely used for osteomyelitis. However, it may have a more attractive side-effect profile than linezolid and deserves further study.

Daptomycin, a cyclic lipopeptide antimicrobial agent, has bactericidal activity against aerobic and facultative gram-positive pathogens. The role of daptomycin in the therapy of patients with osteomyelitis is now established.[38,39] A multicenter retrospective study in Europe of 220 patients with osteomyelitis evaluated the efficacy and safety of daptomycin. Only 0.5% of patients had an elevation of creatine phosphokinase, and 75% of patients had a successful outcome.[38] However, resistance to daptomycin has occurred during prolonged therapy.[40] The role of daptomycin in osteomyelitis caused by methicillin-susceptible *S. aureus* osteomyelitis, compared with β-lactam, has not been assessed.

Oral Agents for Antimicrobial Therapy

A combination of trimethoprim-sulfamethoxazole and rifampin for 8 weeks was compared with parenteral cloxacillin for 6 weeks, followed by oral cloxacillin for 2 weeks in a randomized clinical trial of 50 patients with nonaxial oxacillin-susceptible staphylococcal osteomyelitis. No difference in the outcome was noted between the groups, emphasizing the important role of rifampin when combined with a highly bioavailable agent.[41] Pharmacokinetic interactions among drugs used in combination are increasingly recognized, particularly in those combinations using rifampin. Two small studies provide support for a pharmacologically significant decrease in clindamycin concentrations when the drug is used in combination with rifampin, but no clinical effect has yet been shown.[42,43]

First-generation quinolones, such as ciprofloxacin, have little activity against staphylococci, streptococci, and enterococci and no activity against anaerobes. Levofloxacin has good streptococcal and staphylococcal activity but variable and minimal anaerobic activity. The latest-generation quinolones, such as moxifloxacin, are broad-spectrum antimicrobials with excellent activity against gram-negative and gram-positive organisms and improved anaerobic activity. Increasing awareness of adverse effects such as tendon damage, neuropathy, and other serious complications has led to US Food and Drug Administration (FDA) to urge quinolone use only in serious infections, such as osteomyelitis. Although this class of medications remains an important option for this challenging infection, the benefits and risks must be carefully weighed on a case-by-case scenario.

New Agents for Antimicrobial Therapy

Several new agents with activity against MRSA have become available in the last several years. None of these agents have sufficient published clinical experience to replace existing agents, but they provide off-label therapeutic options in the case of clinical failure or intolerance. Ceftaroline, a fifth-generation cephalosporin that is active against MRSA via penicillin binding protein-2a binding, has been used in the setting of previous clinical failure.[44] The incidence of neutropenia during

ceftaroline use appears to be higher than with other therapy.[45] Limited retrospective reports support the use of telavancin, a lipoglycopeptide administered once daily, for osteomyelitis.[46,47] However, a significantly higher incidence of adverse events, including renal failure, was observed during phase II and III studies for other indications, suggesting that telavancin should be used only when other agents with a better safety profile cannot.[48] Dalbavancin and oritavancin are lipoglycopeptides that have the unique property of significantly prolonged half-lives, administered once weekly. Although they have been approved for skin and soft tissue infection, further study is needed before routine use can be considered for osteomyelitis.

Duration of Antimicrobial Therapy

The optimal duration of antimicrobial therapy in osteomyelitis is unknown because of the few prospective randomized clinical trials assessing the length of antimicrobial therapy in patients with osteomyelitis and the heterogeneous nature of the disease.[49] In experimental models, 4 weeks of therapy was more effective in sterilizing bone than 2 weeks of therapy. Surgical débridement was not part of these models, however, and shorter courses of therapy may be as effective when extensive surgical débridement is accomplished.[10] Because it takes 6 weeks for the débrided bone to be covered by vascularized soft tissue, and because of anecdotal experiences suggesting a higher relapse rate with a short duration of therapy, many experts advocate a total duration of 4 to 6 weeks of parenteral or highly bioavailable oral antimicrobial therapy. When the surgical débridement of all infected bone is complete or the osteomyelitic bone has been resected, some experts advocate short-duration antimicrobial therapy.[50] When stable, patients can be dismissed from the hospital, and parenteral antimicrobial therapy can be continued on an outpatient basis. Use of long-term intravenous catheters, such as peripherally inserted central catheters (PICCs), can facilitate this task.[26,51]

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy has been used as an adjunctive measure for patients with chronic or refractory osteomyelitis.[52–54] It is hypothesized that an adequate oxygen tension is necessary for oxygen-dependent killing of organisms by the polymorphonuclear leukocytes and for fibroblast activity, leading to angiogenesis and wound healing. In addition, hyperbaric oxygen has a direct bactericidal or bacteriostatic effect on obligate anaerobic organisms. The body of evidence does suggest that there might be a favorable role in the promotion of chronic ulcer healing and in the reduction of major limb amputation.[52] Anecdotal experience in humans includes data derived from convenience retrospective cohorts of patients with recurrent and/or refractory osteomyelitis (see Chapter 50). To our knowledge, there are no adequate randomized trials assessing the efficacy of hyperbaric oxygen therapy in humans with chronic or refractory osteomyelitis, and its use in this scenario is still unproven.[53]

OSTEOMYELITIS AFTER A CONTAMINATED OPEN FRACTURE

Contaminated open fractures can lead to the development of osteomyelitis of the fractured bone, typically at the fracture site in 3% to 25% of cases, depending on the type of fracture, the level of contamination, the degree of soft tissue injury, and whether systemic and local antimicrobial therapies have been administered (see Fig. 104.2).[55–59] Patients with open fractures are usually young men in their teens or 20s. The bones of the lower extremity are typically involved, most often the tibia or fibula. Early contamination after the open fracture of bone and soft tissue eventually can lead to the development of osteomyelitis at the fracture site. Untreated, infection ultimately may lead to nonunion of the infected site, chronic osteomyelitis, or amputation.

Microbiology of Osteomyelitis After Contaminated Open Fracture

The microorganisms isolated late in this type of osteomyelitis correlate in 25% with the initial culture results at the time of débridement.[60] A variety of microorganisms have been implicated. Pathogens can include normal skin flora that contaminate the wound, organisms from contaminated soil, or nosocomial pathogens acquired because of the multiple operations that often are required to surgically repair the fracture and surrounding soft tissue envelope. Staphylococci and aerobic gram-negative bacilli are the two most common groups of microorganisms implicated in this type of osteomyelitis. Several other unusual microorganisms, such as enterococci, fungi, and atypical mycobacteria, also have been implicated.

Management of Open Contaminated Fractures to Prevent Osteomyelitis

Current management of open contaminated fractures entails early aggressive wound irrigation and débridement, administration of empirical parenteral antimicrobials, stable fracture fixation, and soft tissue coverage of exposed bone. In one study, a delay of 5 hours in surgical débridement was associated with a higher incidence of infection.[60] In contrast, a well-performed systematic review did not definitively support the need for early débridement for prevention of infection.[61] Despite the lack of clear support in the literature, we favor early débridement if possible, provided it does not have negative consequences from an operative optimization standpoint. Randomized clinical trials performed by Patzakis and colleagues[62] established the efficacy of a short duration of antimicrobial prophylaxis in the prevention of osteomyelitis in patients treated for open contaminated fractures. The use of prolonged antimicrobial therapy for prevention does not decrease the risk of infection and potentially can lead to the development of resistant microorganisms.[63,64] The addition of empirical vancomycin to cover MRSA in this setting may not be warranted.[65] Although the addition of fluoroquinolone or aminoglycoside may decrease the rate of soft tissue infection, the rate of osteomyelitis is not affected and an increase in resistant gram-negative pathogens may result.[66] Cohort studies have shown the efficacy of antibiotic-impregnated polymethyl methacrylate beads temporarily placed in and around the fracture site in the prevention of osteomyelitis after a contaminated open fracture.[67,68] The choice between external versus intramedullary fracture fixation devices in contaminated open fractures is controversial and discussed in detail elsewhere (see Chapter 105).

Signs and Symptoms of Osteomyelitis After Contaminated Open Fracture

Signs and symptoms of infection typically appear several months after an open fracture. The hallmark of osteomyelitis after open fracture is nonunion of the fracture site or poor wound healing after wound closure or soft tissue coverage. Other symptoms, such as local erythema or fever and chills, are less common. MRI or radionuclide imaging studies are typically neither sensitive nor specific for the presence of infection because of the abnormalities created by the recent previous surgery and the presence of foreign bodies.

Management of Osteomyelitis After Contaminated Open Fracture

Management of established osteomyelitis or infected nonunion after an open fracture requires débridement of the surgical site, identification of the causative microorganisms, and pathogen-directed antimicrobial therapy (see Table 104.3). If foreign bodies are retained, long-term oral antimicrobial suppression may be helpful until fracture healing occurs, at which time oral antimicrobial suppression could be discontinued. The use of quinolone and rifampin combinations has been studied in staphylococcal fracture–fixation device infection.[69,70] In sensitive staphylococcal hardware-associated osteomyelitis, a 3- to 6-month course of a quinolone and rifampin eradicated the infection in more than 80% of cases.[69,70] Given the good outcome of patients treated with other antimicrobials and concerns about the effect of quinolones on bone healing, we have not universally adopted this strategy.[13] Others have suggested use of rifampin in combination with other agents, such as linezolid or trimethoprim-sulfamethoxazole, which may avoid the toxicity concerns of quinolones while still using rifampin-based therapy.[71] If recurrence of the infection develops after discontinuation of long-term oral antimicrobial suppression and fracture bone healing, definitive therapy with removal of the foreign bodies and pathogen-directed antimicrobial therapy usually can be then undertaken without

compromising limb function. This therapeutic strategy is in contrast to prosthetic joint infection treated with débridement and retention of components, in which removal of the prosthesis typically compromises limb function.

VERTEBRAL OSTEOMYELITIS AND SPONDYLODISKITIS

Infection of the end plate and the adjacent vertebrae, variably referred to as *spondylodiskitis, disk space infection,* or *vertebral osteomyelitis,* all with or without associated epidural abscess (see Chapter 91) or psoas abscesses, is hematogenous in origin in most cases.[72–74] Potential sources of hematogenous infection are skin and soft tissue infection, genitourinary tract infection, infective endocarditis, infected intravenous sites, intravenous drug abuse, and respiratory tract infection.[73,75] Infection of the disk space and contiguous vertebra also may occur postoperatively.[75] Several studies have established the efficacy of antimicrobial prophylaxis before spinal surgery in reducing the risk of postoperative superficial or deep infection, including vertebral osteomyelitis. In one study by Schnöring and Brock,[76] 0.2% of patients receiving antimicrobial prophylaxis developed a surgical site infection, whereas 2.8% of patients developed surgical site infection when antimicrobial prophylaxis was withheld.

Clinical Signs and Symptoms of Vertebral Osteomyelitis

The clinical presentation of vertebral osteomyelitis includes localized insidious pain and tenderness in the spine area in 90% of patients. Fever is present in less than 50% of patients. Motor and sensory deficits, caused by spinal cord or nerve root compression, are present in 15% of patients.[73–76]

Microbiology of Vertebral Osteomyelitis

S. aureus, coagulase-negative staphylococci, and *Streptococcus* spp. are the most common microorganisms encountered in vertebral osteomyelitis.[73–76] *Mycobacterium tuberculosis* and *Brucella* spondylodiskitis are common in endemic regions.[77,78] Spine infections caused by gram-negative aerobic bacteria and *Candida* spp. are seen more commonly in intravenous drug abusers, immunosuppressed patients, and postoperative patients.[79,80] Immunosuppressed patients with human immunodeficiency virus infection or congenital or iatrogenic immunodeficiencies are increasingly reported with vertebral osteomyelitis caused by nontuberculous mycobacteria, with *Mycobacterium avium* complex and *Mycobacterium xenopi* dominating a review of cases over the years 1961–2014.[81]

Diagnosis of Vertebral Osteomyelitis

The diagnosis of vertebral osteomyelitis requires a high index of suspicion in at-risk patients presenting with compatible signs and symptoms. The goal of the diagnostic evaluation is to determine the extent of infection and identify the organism. Neurologic function and spinal stability always should be assessed carefully. An elevation of the ESR is present in more than 90% of cases, whereas the white blood cell count is elevated in less than 50% of patients.[73–76] Assessing for the presence of concomitant infective endocarditis should be done, especially in patients with bloodstream infection.[82,83] Plain spinal radiographs are not sensitive in the diagnosis of disk space infection. In one study, 32% of radiographs suggested diskitis.[84] MRI has proved to be an invaluable tool in detecting disk space infection and spinal cord compression (Figs. 104.3 and 104.4). Ga-67 citrate scanning seems to be a sensitive and specific method used to diagnose diskitis. In a study of 41 patients with suspected spondylodiskitis, Ga-67 scanning proved to be 100% sensitive, specific, and accurate.[85] We use Ga-67 or CT scanning when MRI cannot be performed and in cases in which MRI is inconclusive. The experience with the use of ^{18}F-fluorodeoxyglucose PET in the diagnosis of vertebral osteomyelitis is limited but appears to be promising.[86] PET/CT was found to improve specificity, positive and negative predictive values, and accuracy compared with stand-alone PET in patients with suspected osteomyelitis or implant-associated infection.[87] A prospective study comparing MRI and PET/CT found comparable sensitivity and specificity between the two modalities for diagnosing vertebral osteomyelitis.[88] However, the superior resolution of MRI allowed better detection of epidural and paravertebral infection, whereas PET/CT more readily allowed identification of areas of metastatic infection. Guidelines from the Infectious Diseases Society of America have been published to assist in the diagnosis and treatment of native vertebral osteomyelitis in adults.[89]

FIG. 104.3 T1-weighted magnetic resonance images show an abnormal signal in the disk between L2 and L3, with associated vertebral osteomyelitis. A fluid collection is located in the posterior part of L2 and L3, resulting in the elevation of the posterior ligament. *Staphylococcus aureus* grew from a computed tomography–guided aspirate.

FIG. 104.4 Angiogram of the lower extremity reveals an occluded bypass graft *(arrow)* in a patient with diabetes mellitus who presented with chronic gangrene and osteomyelitis of the foot.

Microbiologic Diagnosis of Vertebral Osteomyelitis

Accurate microbiologic diagnosis is critical to informing therapeutic decision making. In a significant proportion of patients with *S. aureus* diskitis, the diagnosis is often made through the detection of concomitant *S. aureus* bloodstream infection.[90] If a microbiologic diagnosis is not obtained through blood cultures, percutaneous biopsy should be performed. An analysis of the microbiology in a French prospective multicenter study of 101 patients with microbiologically confirmed vertebral osteomyelitis found that coagulase-negative staphylococci (26%), *S. aureus* (21%), *Streptococcus* spp. (13%), and Enterobacteriaceae (21%) were the most common isolates.[91] Bone biopsy can be challenging, requiring special tools and expertise. The findings of a 10-year retrospective study suggest that inflamed paravertebral soft tissue, even in the absence of abscess, may be a suitable diagnostic target.[92] Image-guided percutaneous biopsy and aspiration has a sensitivity of 38% to 60%.[93,94] If the results for the first aspirate are inconclusive, a repeat aspiration may be performed to optimize the sensitivity of the microbiologic or pathologic diagnosis. In one study, a microbiologic diagnosis was made in 80% of patients when a second biopsy was performed in those with negative cultures at first biopsy.[95] An open or a percutaneous endoscopic procedure should be reserved for patients with a nondiagnostic fluoroscopic-guided aspiration or in patients not responding to empirical antimicrobial therapy.[96]

Therapy for Vertebral Osteomyelitis

The goals of therapy should include eradicating the infection, relieving pain, preserving or restoring neurologic function, and maintaining spinal stability. Complete bed rest is not often necessary. The spine could be externally stabilized with a corset or a body brace. The treatment of vertebral osteomyelitis requires an initial 6-week course of antimicrobial therapy (see Table 104.3). A study found that a 6-week course of therapy was not inferior to a 12-week course.[97] Parenteral antimicrobial treatment may be extended in difficult cases or in cases in which undrained abscesses are being treated and do not resolve after 6 weeks. In a retrospective study from Korea, MRSA infection, undrained paravertebral or psoas abscess, and end-stage renal disease were found to be independent risk factors for recurrence. The authors suggest that in the presence of one of these risks, antibiotic treatment for longer than 8 weeks should be used to lessen the risk of recurrence.[98]

Role of Surgery for Vertebral Osteomyelitis

Surgical therapy is not necessary in most cases. Surgical débridement should be considered in patients with a large paravertebral abscess or an epidural abscesses (Fig. 104.5; also see Chapter 91), when medical management fails, or when the spine is mechanically unstable. In selected cases, percutaneous transpedicular débridement and diskectomy, performed under fluoroscopic guidance, may prevent the progression of bone destruction and deformity in the early stages of vertebral osteomyelitis and spondylodiskitis.[96] The neurologic status of the patient must be monitored closely.

Follow-Up Evaluation for Vertebral Osteomyelitis

Evaluation at the end of therapy should assess for improvement in clinical signs, symptoms, and laboratory markers of infection. Patients with successful treatment should have resolution of the systemic symptoms of infection and improvement in pain, but pain is often not resolved completely. A 25% or greater improvement in ESR and CRP at 4 to 8 weeks, compared with baseline level, is associated with successful treatment.[99,100] Follow-up MRI of patients with vertebral osteomyelitis has a limited role and may give the impression of clinical worsening, even though there otherwise is clinical improvement.[101] We advocate the use of follow-up MRI in patients with persistent elevation of inflammation markers, in patients with persistent pain, or in case of development of new neurologic signs or symptoms.[101] With effective antimicrobial therapy, spontaneous fusion between adjacent infected vertebral bodies requires 12 to 24 months.

FIG. 104.5 Signal changes within the C5 and C6 vertebral bodies and pedicles consistent with bone edema are seen, along with a small anterior epidural collection consistent with diskitis and epidural abscess.

Hardware-Associated Vertebral Infection

Early postoperative hardware-associated spine infection is treated initially with surgical débridement and retention of the hardware (see Chapter 105). Removal of spinal hardware in this situation would compromise the stability of the spine and the spinal cord. In this setting, surgical débridement is followed by a course of parenteral antimicrobial therapy (see Table 104.3).[102] Although not recommended by all experts, parenteral antimicrobial therapy at our institution is typically followed by the use of long-term oral antimicrobial suppression in this situation.[77] Long-term antimicrobial suppression should be continued until there is radiologic evidence of bone vertebral fusion. This modality is highly successful in our institution.[102] Complete bone remodeling and fusion typically are complete after 2 years. At that time, long-term oral suppression may be discontinued, with a low risk of recurrence. If there is recurrence, the spinal hardware can be removed without compromising the stability of the spine.[102] Successful therapy for late postoperative hardware-associated spine infection often involves removal of the hardware, followed by a course of antimicrobial therapy (see Table 104.3).

OSTEOMYELITIS IN PATIENTS WITH DIABETES MELLITUS OR VASCULAR INSUFFICIENCY

Osteomyelitis in patients with diabetes mellitus is typically found in the foot and less often in the hand.[103,104] The economic consequences of this type of osteomyelitis are enormous and extremity amputation is all too common. In 2014 the estimated annual cost of management of diabetic foot ulcers in the United States was $9 billion to $13 billion.[105] Fifteen percent to 25% of patients with diabetes mellitus develop foot ulcers during their lifetime. Of those, up to 24% will develop a soft tissue infection or contiguous osteomyelitis.[106] Several factors can lead to the development of a diabetic foot infection. Neuropathy, vascular insufficiency (see Fig. 104.4), and hyperglycemia can lead to a variety of consequences that ultimately lead to the development of a skin ulcer and subsequently to contiguous osteomyelitis.

Prevention of Diabetic Foot Osteomyelitis

Early recognition and management of factors that can lead to the development of foot ulcers in patients with diabetes mellitus are crucial to the delay or even prevention of osteomyelitis (see Fig. 104.6). In assessing the risk of subsequent foot ulcer in patients with diabetes mellitus, the treating physician should pay special attention to several factors (Table

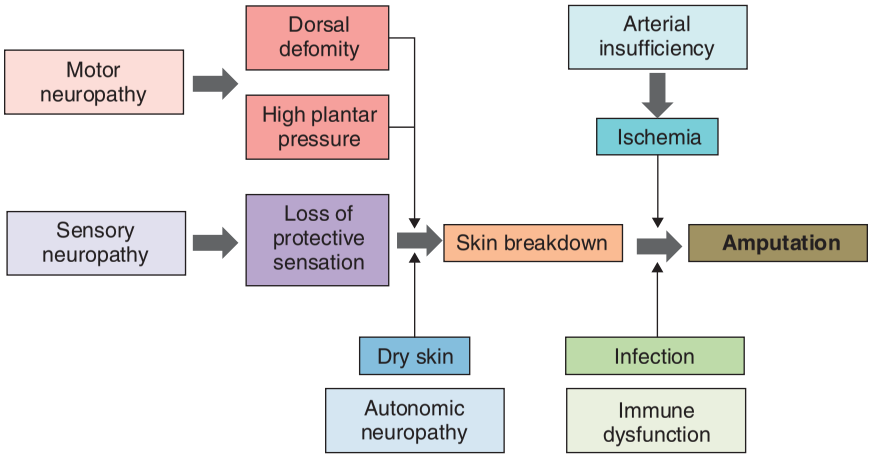

FIG. 104.6 Diagram of the multiple factors that may contribute to the development of diabetic foot infection. *(Modified from Ulbrecht JS, Cavanagh PR, Caputo GM. Foot problems in diabetes: an overview.* Clin Infect Dis. *2004;39(suppl 2):S73–S82.)*

TABLE 104.5 Factors Associated With Increased Risk of Foot Ulcers in Patients With Diabetes Mellitus

Diabetes mellitus duration over 10 years
Poor glucose control
Cardiovascular disease
Renal or retinal complications
Peripheral neuropathy
Evidence of increased local pressure (callus, erythema)
Limited joint mobility
Peripheral vascular disease
Prior history of foot ulcer
Prior history of amputation

104.5). The lower extremity macrovascular and microvascular circulation supply can be assessed through physical examination of the pedal pulses, noninvasive vascular assessments such as Doppler ultrasound, or measurement of transcutaneous oxygen pressures.[50] Patients with diabetes mellitus or vascular insufficiency should have an annual complete foot examination performed by a health care professional.[50] Strict glycemic control and smoking cessation can reduce the rate of progression of vascular diseases and neuropathy. Patients with evidence of foot irritation from local pressure should be offered well-cushioned walking shoes that redistribute the pressure in their feet.[107]

Diagnosis of Osteomyelitis in Patients With Diabetes or Vascular Insufficiency

As discussed earlier, the diagnosis of osteomyelitis in patients with diabetes or vascular insufficiency often requires multiple modalities, including a careful physical assessment of the foot and the ulcer, which can often provide clues to the presence of contiguous osteomyelitis. A chronic ulcer with a surface area of more than 2 cm^2 or a positive probe-to-bone test is associated with high positive predictive value.[108] In a systematic review of 288 pooled cases, the sensitivity of exposed bone or a probe-to-bone test was 60%, and the specificity was 91%. MRI was associated with a pooled sensitivity of 90% and a specificity of 79%.[109] Deep surgical cultures of bone and soft tissue submitted for aerobic and anaerobic cultures often revealed the presence of multiple microorganisms. This can be done by means of open débridement, needle puncture, or transcutaneous bone biopsy.[110] Although the microbiome of diabetic foot wounds may be less diverse than in intact skin,[111] the contribution of this microbiome to wound healing is not yet determined. An evaluation of the microbiome in diabetic foot osteomyelitis comparing 16S rRNA sequencing with conventional microbiologic techniques observed higher rates of anaerobes and gram-positive bacilli with the molecular assay.[112] Population-based surveillance in California from 1995 to 2012 identified an increased incidence of group B *Streptococcus (Streptococcus agalactiae),* with diabetes present in 76.3% of patients with bone infections.[113]

Management of Osteomyelitis in Patients With Diabetes or Vascular Insufficiency

As in other forms of osteomyelitis, combined surgical and medical therapy is most often warranted (see Tables 104.3 and 104.4). Treatment failure is often due to lack of débridement, peripheral vascular disease, and failure to obtain deep cultures before antimicrobial therapy.[103] Pelvic osteomyelitis under pressure ulcers presents many diagnostic and therapeutic challenges. MRI and multiple bone biopsies for culture and histology were obtained in a study from France. Osteomyelitis was associated with the concordance of microbiology and histology, with poor correlation with MRI findings.[114]

In patients with poor arterial vascular supply, revascularization should be done if possible to provide blood flow to the débrided area or to minimize the extent of any amputation that may be required. In this subset of patients, the infected and necrotic bone is usually exposed and surrounded by poorly vascularized soft tissue. Management of dead space and adequate surgical drainage of infected bone and soft tissue often are required. When possible, antimicrobial therapy should be withheld until intraoperative deep cultures have been obtained. Antimicrobials should be administered before culture results, however, in patients with local or systemic signs of an infectious process (cellulitis, acute soft tissue infection, fever, and hemodynamic compromise). In carefully selected cases and when surgical débridement is not done, a prolonged course of antimicrobial therapy for 3 months or more has been shown to be curative and a 6-week duration of therapy may be sufficient.[50,115]

Antimicrobial Therapy for Osteomyelitis in Patients With Diabetes or Vascular Insufficiency

Because most of these infections are polymicrobial, including multiple aerobic and anaerobic microorganisms, broad-spectrum antimicrobial therapy often is required. Multiple antimicrobial regimens have been used, including piperacillin-tazobactam, ampicillin-sulbactam, ertapenem, or other β-lactams combined with metronidazole.[50] A quinolone combined with metronidazole or clindamycin also is considered an acceptable alternative and has excellent oral bioavailability. The efficacy of linezolid in the treatment of diabetic foot infection was evaluated in a large randomized clinical trial. In this study, linezolid with or without aztreonam was compared with an aminopenicillin/β-lactamase inhibitor. The linezolid arm was comparable to the aminopenicillin arm in terms of safety, clinical efficacy, and microbiologic efficacy in this particular study.[116] Surgical therapy was performed when clinically indicated. However, bone marrow suppression, peripheral

neuropathy, and optic neuritis are always a concern in prolonged linezolid therapy.

Depending on the level of surgical débridement and amputation, the duration of antimicrobial therapy varies from a few days to several weeks.[50] Some experts recommend that antimicrobial therapy be extended until the soft tissue defect and the skin have completely healed. A small (20 patients per arm) prospective, randomized trial of 6 versus 12 weeks of antibiotic therapy without surgery found no difference in the outcome of complete and persistent healing of the wound and no need for surgical therapy at the end of follow-up (12 months).[115]

ACUTE HEMATOGENOUS OSTEOMYELITIS

Hematogenous seeding of bones, albeit rare, potentially can affect any bone in the body. Acute hematogenous osteomyelitis of long bones occurs mainly in prepubertal children, elderly patients, intravenous drug abusers, and patients with indwelling central catheters. Hematogenous seeding of an intervertebral disk space can occur in adults and was discussed earlier. This section discusses mainly acute hematogenous osteomyelitis in prepubertal children.

Pathophysiology of Acute Hematogenous Osteomyelitis

Acute hematogenous osteomyelitis involves mostly the metaphyses of long bones (Cierny-Mader classification stage I). The tibia or femur is affected in most cases.[117–119] The infection can involve multiple osseous sites. Because the infection is not confined to the metaphyses, approximately half of cases of neonatal osteomyelitis also have involvement of the adjacent joint with development of septic arthritis. The predilection of infection to the metaphyseal region is explained by its peculiar anatomy.[120,121] Capillary ends of the nutrient artery make sharp loops under the growth plate. This nonanastomosing capillary system feeds into large venous sinusoids, where the blood flow becomes slow and turbulent. An obstruction of these capillaries can lead to an area of avascular necrosis. Metaphyseal capillaries lack phagocytic lining cells. Any minor trauma can lead to the development of a small hematoma, vascular obstruction, and subsequent bone necrosis. This area can be seeded from a transient bacteremia. The acute infection initially produces an inflammatory infiltration, increased bone pressure, decreased pH, and decreased oxygen tension. These factors compromise the medullary circulation and enhance the spread of infection. In infants, the infection may proceed laterally through the bone cortex or through the epiphysis and joint surfaces through capillaries that cross the growth plate.

Microbiology of Acute Hematogenous Osteomyelitis

The most common microorganisms isolated in cases of prepubertal hematogenous osteomyelitis are *S. aureus, Kingella kingae,* and *Streptococcus pyogenes.*[122] *Streptococcus pneumoniae* continues to be an important cause of hematogenous osteomyelitis, but incidence has significantly declined with immunization improvements.[123] *Haemophilus influenzae* type b, historically a common cause of long bone osteomyelitis, has become exceedingly rare since the development and widespread use of an effective vaccine in children.[124] Osteoarticular infection may be the first manifestation of disease caused by the *Streptococcus bovis* group *(Streptococcus gallolyticus).* The same caution with regard to concomitant colonic malignancy exists with osteomyelitis as with endocarditis, with 46 of 64 (71.9%) endoscopies performed in patients with osteoarticular infection showing colonic neoplasm.[125] Osteomyelitis in neonates results from hematogenous spread, especially in infants with indwelling central venous catheters. Common causative organisms in osteomyelitis of the neonate are organisms that frequently cause neonatal sepsis, such as group B *Streptococcus* spp. and *Escherichia coli. Candida* spp. and *Pseudomonas aeruginosa* are more commonly encountered in intravenous drug abusers and patients with indwelling central catheters.

In children, the diagnosis often is made in a patient with compatible radiologic and clinical findings with positive blood cultures. In adults, CT-guided aspiration or an open biopsy is often necessary to establish a definitive diagnosis.

Management of Acute Hematogenous Osteomyelitis

Most cases of acute hematogenous osteomyelitis in children can be treated with antimicrobial therapy alone.[124] Surgical débridement and intramedullary reaming are indicated if the diagnosis is in doubt, the patient has not responded clinically to antimicrobial therapy within 48 hours, infection extends into the joint, or an adequate course of antimicrobial therapy fails to cure the infection. After microbiologic specimens have been obtained, empirical antimicrobial therapy is started to cover clinically suspected organisms. When an organism is identified, the antimicrobial therapy can be changed accordingly (see Table 104.3). Switching from parenteral therapy to oral antimicrobial therapy can be done when the patient is afebrile and able to tolerate oral antimicrobials. Oral antimicrobial therapy should be given to compliant patients with close follow-up. A retrospective analysis of postdischarge antibiotics used in children and adolescents with acute osteomyelitis found comparable efficacy of oral versus intravenous antibiotics.[126] In that study of 2060 children and adolescents, 14% of the group discharged on intravenous antibiotics returned to the emergency department or required readmission secondary to complications of PICC. The typical duration of antimicrobial therapy in children is 3 weeks (see Table 104.3). In a study published in 2013, a shorter duration of antimicrobial therapy (i.e., 1 week) was compared with a 2-week duration in 53 pediatric patients with acute osteomyelitis. No difference in the outcome was observed after a median follow-up of 11.5 months.[119] Dosages of antimicrobials should be adapted to the pediatric population. Quinolones are contraindicated in pediatric patients. In adults with acute hematogenous osteomyelitis, surgical therapy often is required, followed by appropriate antimicrobial therapy based on culture and sensitivity data.

SAPHO SYNDROME

SAPHO, an acronym for *s*ynovitis, *a*cne, *p*lantar pustulosis, *h*yperostosis, and *o*steitis, is an autoinflammatory disease of unknown cause. Although incompletely understood, chronic recurrent multifocal osteomyelitis (CRMO), chronic nonbacterial osteitis, and SAPHO may all be different manifestations of the same disease. SAPHO syndrome was first described in 1972 by Giedion and coworkers.[127,128] The pathogenesis of this disease is unclear. Studies have implicated several genetic factors in the pathophysiology of this disease. Local swelling and tenderness of affected bones is often present. Systemic symptoms of fever, weight loss, and generalized malaise are rare. Osteitis typically is multifocal and affects several bones, including the chest wall bones (63%), pelvis (40%), and spine (33%).[129]

Bones of the lower limbs are affected in only 6% of cases. The mean number of active lesions per patient is five. The disease is self-limited, with spontaneous intermittent periods of exacerbation and remission. The differential diagnosis includes infectious osteomyelitis, bone malignancy, and other inflammatory arthritides. Patients require bone biopsy and cultures for diagnosis to exclude infectious osteomyelitis.

Diagnosis of SAPHO Syndrome

There are no specific laboratory tests to diagnose SAPHO syndrome. The ESR is increased in 65% of cases. Bone radiographs may show lytic erosions similar to those of infectious osteomyelitis affecting the metaphysis. With time, reactive hyperostosis can develop. Histopathology typically is nonspecific, with a combination of acute and chronic inflammatory cells. Cultures of biopsy material are typically negative for bacteria, fungi, or mycobacteria.[130] The role of *Propionibacterium acnes* in the pathophysiology of SAPHO syndrome is intriguing and may require additional investigation.[130]

Management of SAPHO Syndrome

Several therapeutic modalities, including nonsteroidal antiinflammatory drugs, pamidronate, glucocorticoids, sulfadiazine, methotrexate, tumor necrosis factor-α inhibitors, and interferon-γ (IFN-γ), have been used in case reports and small case series.[129–134] The role of continuous use of azithromycin and doxycycline was assessed in 27 patients who were treated for 16 weeks in a study by Assmann and coworkers.[130]

Patients were assessed after discontinuation of antimicrobial therapy. MRI findings, skin activity, and overall health assessment improved while patients were on antibiotics and worsened after discontinuation of antimicrobial therapy, suggesting a role for chronic use of antimicrobials.[130]

OTHER FORMS OF OSTEOMYELITIS: SPECIFIC HOSTS, UNUSUAL LOCATIONS, OR UNUSUAL ORGANISMS

Osteitis Pubis

Osteitis pubis is an infection of the symphysis pubis. It was recognized as a complication in the early era of gynecourologic surgery. Early reports postulated incorrectly that this disease was not infectious because of the nonresponse to antimicrobials and the "nonvirulent organisms" recovered during cultures. The disease is encountered after a variety of urologic and gynecologic surgical procedures, including Marshall-Marchetti-Krantz urethropexy, prolonged catheterization, inguinal hernia repair, vaginal delivery, and prostatectomy or radiotherapy for prostate cancer.[135–142] *S. aureus, Enterococcus* spp., *E. coli, Pseudomonas* spp., and *Proteus* spp. are the most commonly encountered organisms.

Sterile Osteitis Pubis

Some patients might present with a sterile form of osteitis pubis. It is believed that this form is due to an aseptic inflammation that could be triggered by surgery, by bone infarction, or in athletes. Most patients present with suprapubic pain and difficulty and pain with ambulation. In one study, the time between surgery and the diagnosis ranged from 2 to 18 months.[143] Fever and leukocytosis rarely are present.[144] An elevated ESR (>20 mm/h) is present in 67% of patients.[144] Plain radiographs may be normal early in the disease. Radiographs performed 6 months later can reveal pubic bone sclerosis, widening of the joint spaces, and rarefaction. CT and MRI are more sensitive than plain radiography and can define the soft tissue much better. Bone or indium-labeled white blood cell scanning is sensitive. Fine-needle aspiration is sometimes helpful.

The aseptic form of osteitis pubis could be managed with nonsteroidal antiinflammatory drugs and corticosteroids. Antimicrobial therapy should be administered in all other cases. In one study, surgical débridement of infected bone was required in more than 70% of cases.[144]

Osteomyelitis of the Clavicle

Osteomyelitis of the clavicle represents less than 3% of osteomyelitis cases.[117–119,145] It may be hematogenous or related to subclavian vein catheterization or neck surgery.[146] *S. aureus* is the most common organism.[114] A variety of other microorganisms have been described, including gram-negative bacteria and *M. tuberculosis*.[145,147] Given the nontraumatic nature, most cases of clavicular osteomyelitis present a therapeutic challenge. The disease may manifest with acute local pain and swelling with positive blood cultures (i.e., *S. aureus*) or may be more chronic and indolent in nature (i.e., *M. tuberculosis*). In one study, the clinical duration of the symptoms ranged from 2 weeks to 1.5 years.[148] All patients typically presented with clavicular site pain. Fever, localized swelling or a mass, and soft tissue abscesses were present in 60%, 30%, and 30% of cases, respectively.[148] Plain radiographs of the clavicle can show sclerotic or lytic changes. Acute cases secondary to *S. aureus* can be treated with parenteral antimicrobial therapy alone (see Table 104.3). Chronic cases should be treated with surgical débridement, followed by antimicrobial therapy.

Osteomyelitis in Hemodialysis Patients

Metastatic infections complicate 7% of tunneled catheter–related bloodstream infections in dialysis patients. These metastatic infections usually affect the disk space, epidural space, and joint space.[149] Because of a higher rate of *S. aureus* colonization in this patient population, most cases of hematogenous osteomyelitis are due to this microorganism. Oxacillin resistance is common among *S. aureus* isolates in these patients. Advanced diabetes mellitus and peripheral vascular disease are common among patients undergoing hemodialysis. These conditions put these patients at risk for contiguous osteomyelitis of the extremities (see "Osteomyelitis in Patients With Diabetes Mellitus or Vascular Insufficiency").

Osteomyelitis in Patients With Sickle Cell Disease

Patients with sickle cell disease are at increased risk for osteoarticular infections. Sites of bony infarction result from recurrent episodes of vasoocclusion in an expanded marrow space. These sites of necrotic bone are at risk for hematogenous seeding.[150] Acute and long bone osteomyelitis and septic arthritis are the most commonly encountered syndromes. In a large cohort study of 299 patients with homozygous sickle cell anemia in France, the prevalence of osteomyelitis was 12%.[151] *Salmonella* spp. and *S. aureus* remain the most commonly encountered microorganisms in sickle cell anemia patients with osteomyelitis.[152] Most patients are children.[152,153] Although osteomyelitis could be multifocal in this setting, long bones are commonly affected.

The differentiation between bone infarction and osteomyelitis could be challenging because their clinical and radiologic presentations are similar. A history of focalized bone pain and prolonged leukocytosis suggests osteomyelitis.[153] Sequential radionuclide bone marrow and bone scans can aid in the differentiation process.[154] CT-guided aspirate or an open biopsy with cultures sometimes is needed for a more definitive diagnosis, but the procedure can infect previously sterile, infarcted bone. Surgical and medical therapies are similar to those for osteomyelitis in patients without sickle cell disease. Empirical antimicrobial therapy should be directed against *Salmonella* and *S. aureus*.[155]

Gaucher Disease

An acute bone crisis, typically affecting the tibia in patients with Gaucher disease, the most prevalent lysosomal storage disorder, is accompanied by fever, intense local pain, and signs of inflammation. Intravascular activation of coagulation is postulated to be the cause of the ischemic insult to the bone. Bone crisis may occur in stable and treated patients with enzyme replacement therapy. Like patients with SS-hemoglobin disease (sickle cell anemia), these patients may be incorrectly considered to have acute osteomyelitis and, if biopsy is performed, may be at risk for developing osteomyelitis at the biopsy site.[156]

Osteomyelitis in Injection Drug Users

Osteoarticular infections occur more commonly in injection drug users (see Chapter 312).[157] Pathogens can reach the bones via hematogenous routes or through contiguous or direct inoculation. Multiple skeletal sites can be affected. Unusual sites of infection outside this setting are common in these patients, such as sternoclavicular, sternochondral joint, sacroiliac joint, and pubic symphysis. *S. aureus, Pseudomonas* spp., and *Candida* spp. are the most commonly encountered organisms in these patients. *M. tuberculosis* can cause vertebral osteomyelitis in these patients. *Eikenella corrodens,* a normal oral flora microorganism, can cause osteomyelitis in injection drug users who lick the needle tip or the skin before injection ("needle licker osteomyelitis").[157] Surgical and medical therapy for osteomyelitis in these patients is similar to therapy in other groups with osteomyelitis. OPAT and central venous access catheters should be used with caution in these patients, with some data suggesting an increased risk of complications.[158,159]

Skeletal Mycobacterial Infection

Extrapulmonary disease represents 20% of all tuberculosis (see Chapter 249). Infection of the musculoskeletal system represents 1% to 5% of all tuberculosis cases. Osteomyelitis caused by *M. tuberculosis* often affects the spine or a paraarticular focus. Most cases are the result of a hematogenous spread from a pulmonary source.[160,161]

The clinician should consider tuberculous osteomyelitis in patients with a past medical history of treated or untreated tuberculosis with new back pain, patients with a known positive tuberculin skin test or gamma release assay, young patients, patients coming from endemic areas with chest radiographic findings consistent with active tuberculosis

or old healed tuberculosis, patients with a household member who had tuberculosis, patients with negative bacterial cultures, or patients whose biopsy specimen of infected bone shows granulomatous inflammation. Clinical features of osteomyelitis caused by *M. tuberculosis* are pain and swelling with abscess and sinus formation. Radiographs reveal irregular cavities and areas of bone destruction with little surrounding sclerosis. Because of the presence of a sinus tract, secondary bacterial infection does occur, although infrequently.[161]

Vertebral Tuberculosis (Pott disease)

Vertebral osteomyelitis caused by *M. tuberculosis,* also called *Pott disease,* is among the most common osteoarticular manifestations of tuberculosis. In this form of vertebral osteomyelitis, in contrast to bacterial vertebral osteomyelitis, systemic symptoms are often absent. Back pain or stiffness is commonly the only symptom, and a delay in the diagnosis is often the norm. In 50% of patients with spinal tuberculosis, MRI reveals paravertebral soft tissue abscesses in addition to the bone lesion. The infection has a predilection for the anterior superior or inferior angles of the vertebral bodies, especially in the early phases of the disease.[160,162] Characteristics and challenges of the diagnosis and course of the disease are presented in a multinational report of 314 patients with a presumed diagnosis of spinal tuberculosis from high-prevalence countries (Egypt, Albania, Greece, and Turkey). Time from onset of symptoms to diagnosis was 78 days. Lumbar disease was most common (56%), followed by thoracic (49%) and thoracolumbar involvement (13%). Of 200 histopathologic examinations, 74% were consistent with tuberculosis, but a causative agent was cultured in only 41%. Mortality was 2%, but 25% developed sequelae, including structural abnormalities (kyphosis, gibbus deformity, scoliosis) and neurologic problems (paraparesis, paraplegia, and loss of sensation).[163] In contrast, in Denmark, the time from symptoms to diagnosis of tuberculosis was 19.5 days for spinal disease and 28 days for other bone and joint manifestations. Culture was diagnostic in 87%. Sequelae were present in 57% of spinal cases, with overall mortality of 25.5% among Danes compared with 1.3% among immigrants.[164]

Diagnosis of Tuberculous Osteomyelitis

Significant overlap in imaging appearances between tuberculous osteomyelitis and other forms of osteomyelitis exists. The diagnosis should rely on the presence of *M. tuberculosis* on stain or culture of a biopsy specimen. Chest radiographs show an abnormality in less than 50% of patients with musculoskeletal tuberculosis but should be obtained routinely because the existence of concomitant pulmonary tuberculosis has infection-control ramifications and may provide for an alternative area from which to obtain culture specimens. Therapy for skeletal tuberculosis is discussed in Chapter 249.

Nontuberculous Mycobacterial Osteomyelitis

Osteoarticular infections with nontuberculous mycobacteria also can occur. They are commonly seen in immunocompromised patients[165] or after contamination of a wound after trauma or surgery. *Mycobacterium marinum, Mycobacterium avium-intracellulare, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium kansasii, and M. xenopi* all have been associated with infection.[165–170] Members of the *Mycobacterium terrae* complex (*M. arupense, M. heraklionense*, and a newly proposed species, *M. virginiense*), but not *M. terrae* sensu strictu, have been associated with tenosynovitis and osteomyelitis in the United States.[171] Disseminated osteoarticular infection with *Mycobacterium bovis* after Calmette-Guérin bacillus vaccination or intravesicular installation of Calmette-Guérin bacillus also has been reported.[172] Children and young adults with unexplained disseminated nontuberculous mycobacterial infections should be tested for the presence of inherited deficiency in the receptor for IFN-γR1 or interleukin (IL)-12β1.

Medical therapy alone is often curative, although in selected cases, surgical débridement is required. Antimicrobial agents typically used in the treatment of osteoarticular infection caused by atypical mycobacteria are the same as agents used to treat infection at other sites and are discussed in Chapters 251 and 252.

Fungal Osteomyelitis

Osteomyelitis caused by fungi is uncommon. Several observational studies and case reports have been published.[173–179] Bone lesions are most common in blastomycosis, disseminated coccidioidomycosis, and extracutaneous sporotrichosis but are seen occasionally in cryptococcosis, candidiasis, and aspergillosis. A survey of cases of spinal coccidioidomycosis collected over 50 years in the American Southwest noted that men and African Americans were disproportionately affected. A review of the management suggested that surgical therapy is indicated for mechanical instability, neurologic deficit, medically intractable pain, or progression despite antifungal therapy, which usually needs to be continued for years.[180] The typical epidemiologic risk factors and host characteristics that predispose to mycoses often provide clues as to the fungal etiology. Although most fungal osteomyelitis is hematogenous, trauma with contamination of a wound is a risk factor for fungal osteomyelitis caused by fungi, including *Scedosporium apiospermum (Pseudallescheria boydii), Lomentospora (Scedosporium) prolificans,* and *Fusarium* spp. Mold infections other than *Aspergillus* are most often associated with trauma in children and with surgery in adults.[181] Hematogenous fungal osteomyelitis usually manifests clinically as a "cold abscess" and radiologically as a well-defined osteolytic lesion with adjacent soft tissue abscess. In contrast, extracutaneous sporotrichosis causes patchy bone loss and commonly extends to contiguous joints. Surgical débridement of contiguous soft tissue should be done in patients with large collections of pus, but the role of surgery is usually limited to biopsy for diagnosis. Therapy for specific mycoses is discussed in Chapters 256 to 268.

Brodie Abscess

Brodie abscess refers to a chronic localized bone abscess. Patients with subacute cases may present with fever, pain, and periosteal elevation, whereas patients with chronic Brodie abscess are often afebrile and present with long-standing dull pain. The most common site of involvement is the distal part of the tibia. The lesion is typically single and located near the metaphysis. Of patients, 75% are younger than 25 years. Surgical débridement and culture-directed antibiotics are often curative. Cultures may be negative.

Culture-Negative Osteomyelitis

Rarely, bone culture specimens are sterile despite clinical, radiologic, and pathologic evidence of osteomyelitis. Brodie abscess and bone infarcts caused by Gaucher disease or sickle cell disease should be considered. At our institution, most of these cases are due to prior use of antimicrobial therapy. For indolent cases not responding to therapy, consideration should be given to stopping antibiotics and waiting for at least 1 month before repeating the culture.[182] Antimicrobial therapy may slow the growth of ordinarily hardy organisms.[183] When aerobic and anaerobic bacterial specimens are sterile, cultures should be obtained for fungi and mycobacteria. In selected cases, polymerase chain reaction analysis using 16S rRNA gene primers with a broad specificity for detecting bacterial DNA in bone and purulent material can be helpful.[183] If all cultures are negative, we believe that the antimicrobial regimen should be designed to cover the commonly encountered organisms that are clinically suspected, taking into account the history of prior use of antimicrobial agents.

SUMMARY

Despite important medical and surgical advances in management of patients, osteomyelitis remains extremely difficult to treat. The relapse rate can be as high as 20%. The optimal management of osteomyelitis requires a multidisciplinary team of physicians, including an orthopedic surgeon, neurosurgeon, oral surgeon, plastic surgeon, vascular surgeon, invasive radiologist, and infectious disease specialist. The usual goal of therapy is the eradication of the infection and restoration of function. Treatment of chronic osteomyelitis usually requires aggressive surgical débridement and prolonged antimicrobial therapy.

Key References

The complete reference list is available online at Expert Consult.

1. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393–407.
2. Mader JT, Shirtliff M, Calhoun JH. Staging and staging application in osteomyelitis. *Clin Infect Dis*. 1997;25:1303–1309.
16. Hartmann A, Eid K, Dora C, et al. Diagnostic value of 18F-FDG PET/CT in trauma patients with suspected chronic osteomyelitis. *Eur J Nucl Med Mol Imaging*. 2007;34:704–714.
17. Termaat MF, Raijmakers PG, Scholten HJ, et al. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2005;87:2464–2471.
18. Kapoor A, Page S, Lavalley M, et al. Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. *Arch Intern Med*. 2007;167:125–132.
22. Harik NS, Smeltzer MS. Management of acute hematogenous osteomyelitis in children. *Expert Rev Anti Infect Ther*. 2010;8:175–181.
26. Paladino JA, Poretz D. Outpatient parenteral antimicrobial therapy today. *Clin Infect Dis*. 2010;51(suppl 2):S198–S208.
30. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285–292.
37. Ashizawa N, Tsuji Y, Kawago K, et al. Successful treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis with combination therapy using linezolid and rifampicin under therapeutic drug monitoring. *J Infect Chemother*. 2016;22:331–334.
38. Seaton RA, Malizos KN, Viale P, et al. Daptomycin use in patients with osteomyelitis: a preliminary report from the EU-CORESM database. *J Antimicrob Chemother*. 2013;68:1642–1649.
40. Hagiya H, Haruki Y, Uchida T, et al. Emergence of daptomycin-resistant *Staphylococcus aureus* during treatment. *Intern Med*. 2016;55:73–78.
41. Euba G, Murillo O, Fernández-Sabé N, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. *Antimicrob Agents Chemother*. 2009;53:2672–2676.
42. Curis E, Pestre V, Jullien V, et al. Pharmacokinetic variability of clindamycin and influence of rifampicin on clindamycin concentration in patients with bone and joint infections. *Infection*. 2015;43:473–481.
43. Bernard A, Kermarrec G, Parize P, et al. Dramatic reduction of clindamycin serum concentration in staphylococcal osteoarticular infection patients treated with the oral clindamycin-rifampicin combination. *J Infect*. 2015;71:200–206.
49. Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences and lessons to be drawn. *Expert Opin Pharmacother*. 2013;14:723–734.
50. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.
52. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. *PM R*. 2009;1:471–489.
56. DeLong WG Jr, Born CT, Wei SY, et al. Aggressive treatment of 119 open fracture wounds. *J Trauma*. 1999;46:1049–1054.
67. Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg Br*. 1995;77:93–97.
70. Trampuz A, Widmer AF. Infections associated with orthopedic implants. *Curr Opin Infect Dis*. 2006;19:349–356.
72. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022–1029.
73. Fantoni M, Trecarichi EM, Rossi B, et al. Epidemiological and clinical features of pyogenic spondylodiscitis. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):2–7.
74. Weissman S, Parker RD, Siddiqui W, et al. Vertebral osteomyelitis: retrospective review of 11 years experience. *Scand J Infect Dis*. 2014;46:193–199.
75. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis*. 2002;34:1342–1350.
81. Kim CJ, Kim UJ, Kim HB, et al. Vertebral osteomyelitis caused by non-tuberculous mycobacteria: predisposing conditions and clinical characteristics of six cases and a review of 63 cases in the literature. *Infect Dis (Lond)*. 2016;48:509–516.
84. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. *QJM*. 2001;94:465–470.
86. Treglia G, Focacci C, Caldarella C, et al. The role of nuclear medicine in the diagnosis of spondylodiscitis. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):20–25.
87. Wenter V, Müller JP, Albert NL, et al. The diagnostic value of [(18)F]FDG PET for the detection of chronic osteomyelitis and implant-associated infection. *Eur J Nucl Med Mol Imaging*. 2016;43:749–761.
89. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61:e26–e46.
91. Desoutter S, Cottier JP, Ghout I, et al. Susceptibility pattern of microorganisms isolated by percutaneous needle biopsy in nonbacteremic pyogenic vertebral osteomyelitis. *Antimicrob Agents Chemother*. 2015;59:7700–7706.
92. Chang CY, Simeone FJ, Nelson SB, et al. Is biopsying the paravertebral soft tissue as effective as biopsying the disk or vertebral endplate? 10-year retrospective review of CT-guided biopsy of diskitis-osteomyelitis. *AJR Am J Roentgenol*. 2015;205:123–129.
93. Kim BJ, Lee JW, Kim SJ, et al. Diagnostic yield of fluoroscopy-guided biopsy for infectious spondylitis. *AJNR Am J Neuroradiol*. 2013;34:233–238.
95. Gras G, Buzele R, Parienti JJ, et al. Microbiological diagnosis of vertebral osteomyelitis: relevance of second percutaneous biopsy following initial negative biopsy and limited yield of post-biopsy blood cultures. *Eur J Clin Microbiol Infect Dis*. 2014;33:371–375.
96. Yang SC, Fu TS, Chen LH, et al. Percutaneous endoscopic discectomy and drainage for infectious spondylitis. *Int Orthop*. 2007;31:367–373.
97. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet*. 2015;385:875–882.
98. Park KH, Cho OH, Lee JH, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. *Clin Infect Dis*. 2016;62:1262–1269.
101. Kowalski TJ, Berbari EF, Huddleston PM, et al. Do follow-up imaging examinations provide useful prognostic information in patients with spine infection? *Clin Infect Dis*. 2006;43:172–179.
102. Kowalski TJ, Berbari EF, Huddleston PM, et al. The management and outcome of spinal implant infections: contemporary retrospective cohort study. *Clin Infect Dis*. 2007;44:913–920.
106. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999;22:382–387.
108. Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA*. 2008;299:806–813.
109. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis*. 2008;47:519–527.
112. van Asten SA, La Fontaine J, Peters EJ, et al. The microbiome of diabetic foot osteomyelitis. *Eur J Clin Microbiol Infect Dis*. 2016;35:293–298.
113. Smith EM, Khan MA, Reingold A, et al. Group B streptococcus infections of soft tissue and bone in California adults, 1995-2012. *Epidemiol Infect*. 2015;143:3343–3350.
114. Brunel AS, Lamy B, Cyteval C, et al. Diagnosing pelvic osteomyelitis beneath pressure ulcers in spinal cord injured patients: a prospective study. *Clin Microbiol Infect*. 2016;22:267.e1–267.e8.
115. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care*. 2015;38:302–307.
116. Lipsky BA, Itani K, Norden C. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. *Clin Infect Dis*. 2004;38:17–24.
117. Copley LA, Kinsler MA, Gheen T, et al. The impact of evidence-based clinical practice guidelines applied by a multidisciplinary team for the care of children with osteomyelitis. *J Bone Joint Surg Am*. 2013;95:686–693.
119. Bouchoucha S, Drissi G, Trifa M, et al. [Epidemiology of acute hematogenous osteomyelitis in children: a prospective study over a 32 months period]. *Tunis Med*. 2012;90:473–478.
120. Kaplan SL. Osteomyelitis in children. *Infect Dis Clin North Am*. 2005;19:787–797, vii.
124. Peltola H, Pääkönen M. Acute osteomyelitis in children. *N Engl J Med*. 2014;370:352–360.
125. García-País MJ, Rabuñal R, Armesto V, et al. *Streptococcus bovis* septic arthritis and osteomyelitis: a report of 21 cases and a literature review. *Semin Arthritis Rheum*. 2016;45:738–746.
126. Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for post discharge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169:120–128.
128. Kundu BK, Naik AK, Bhargava S, et al. Diagnosing the SAPHO syndrome: a report of three cases and review of the literature. *Clin Rheumatol*. 2013;32:1237–1243.
129. Beretta-Piccoli BC, Sauvain MJ, Gal I, et al. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature. *Eur J Pediatr*. 2000;159:594–601.
136. Choi H, McCartney M, Best TM. Treatment of osteitis pubis and osteomyelitis of the pubic symphysis in athletes: a systematic review. *Br J Sports Med*. 2011;45:57–64.
143. Graham CW, Dmochowski RR, Faerber GJ, et al. Pubic osteomyelitis following bladder neck surgery using bone anchors: a report of 9 cases. *J Urol*. 2002;168:2055–2057, discussion 2057–2058.
148. Gerscovich EO, Greenspan A. Osteomyelitis of the clavicle: clinical, radiologic, and bacteriologic findings in ten patients. *Skeletal Radiol*. 1994;23:205–210.
160. Trecarichi EM, Di Meco E, Mazzotta V, et al. Tuberculous spondylodiscitis: epidemiology, clinical features, treatment, and outcome. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):58–72.
163. Batirel A, Erdem H, Sengoz G, et al. The course of spinal tuberculosis (Pott disease): results of the multinational, multicentre Backbone-2 study. *Clin Microbiol Infect*. 2015;21:1008.e9–1008.e18.
164. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
171. Vasireddy R, Vasireddy S, Brown-Elliott BA, et al. *Mycobacterium arupense, Mycobacterium heraklionense,* and a newly proposed species, "*Mycobacterium virginiense*" sp. nov., but not *Mycobacterium nonchromogenicum*, as species of the *Mycobacterium terrae* complex causing tenosynovitis and osteomyelitis. *J Clin Microbiol*. 2016;54:1340–1351.
172. Abu-Nader R, Terrell CL. *Mycobacterium bovis* vertebral osteomyelitis as a complication of intravesical BCG use. *Mayo Clin Proc*. 2002;77:393–397.
175. Gamaletsou MN, Kontoyiannis DP, Sipsas NV, et al. *Candida* osteomyelitis: analysis of 207 pediatric and adult cases (1970-2011). *Clin Infect Dis*. 2012;55:1338–1351.
180. Martirosyan NL, Skoch JM, Zaninovich O, et al. A paradigm for the evaluation and management of spinal coccidioidomycosis. *Surg Neurol Int*. 2015;6:107.
181. Taj-Aldeen SJ, Rammaert B, Gamaletsou M, et al. Osteoarticular infections caused by non-*Aspergillus* filamentous fungi in adult and pediatric patients: a systematic review. *Medicine (Baltimore)*. 2015;94:e2078.

References

1. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393–407.
2. Mader JT, Shirtliff M, Calhoun JH. Staging and staging application in osteomyelitis. *Clin Infect Dis*. 1997;25: 1303–1309.
3. Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med*. 1997;336:999–1007.
4. Norden CW. Lessons learned from animal models of osteomyelitis. *Rev Infect Dis*. 1988;10:103–110.
5. Lew DP, Waldvogel FA. Osteomyelitis. *Lancet*. 2004;364:369–379.
6. Ciampolini J, Harding KG. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? *Postgrad Med*. 2000;76:479–483.
7. Ou JJ, Drilling AJ, Cooksley C, et al. Reduced innate immune response to a *Staphylococcus aureus* small colony variant compared to its wild-type parent strain. *Front Cell Infect Microbiol*. 2016;6:187.
8. Tuchscherr L, Kreis CA, Hoerr V, et al. *Staphylococcus aureus* develops increased resistance to antibiotics by forming dynamic small colony variants during chronic osteomyelitis. *J Antimicrob Chemother*. 2016;71:438–448.
9. Muller C, Zielinski CC, Passl R, et al. Divergent patterns of leucocyte locomotion in experimental post-traumatic osteomyelitis. *Br J Exp Pathol*. 1984;65:299–303.
10. Norden CW, Shinners E, Niederriter K. Clindamycin treatment of experimental chronic osteomyelitis due to *Staphylococcus aureus*. *J Infect Dis*. 1986;153:956–959.
11. Norden CW. Experimental chronic staphylococcal osteomyelitis in rabbits: treatment with rifampin alone and in combination with other antimicrobial agents. *Rev Infect Dis*. 1983;5(suppl 3):S491–S494.
12. Shirtliff ME, Mader JT, Calhoun J. Oral rifampin plus azithromycin or clarithromycin to treat osteomyelitis in rabbits. *Clin Orthop Relat Res*. 1999;359:229–236.
13. Huddleston PM, Steckelberg JM, Hanssen AD, et al. Ciprofloxacin inhibition of experimental fracture healing. *J Bone Joint Surg Am*. 2000;82:161–173.
14. Perry AC, Prpa B, Rouse MS, et al. Levofloxacin and trovafloxacin inhibition of experimental fracture-healing. *Clin Orthop Relat Res*. 2003;414:95–100.
15. Haleem AA, Rouse MS, Lewallen DG, et al. Gentamicin and vancomycin do not impair experimental fracture healing. *Clin Orthop Relat Res*. 2004;427:22–24.
16. Hartmann A, Eid K, Dora C, et al. Diagnostic value of 18F-FDG PET/CT in trauma patients with suspected chronic osteomyelitis. *Eur J Nucl Med Mol Imaging*. 2007;34:704–714.
17. Termaat MF, Raijmakers PG, Scholten HJ, et al. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2005;87:2464–2471.
18. Kapoor A, Page S, Lavalley M, et al. Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. *Arch Intern Med*. 2007;167:125–132.
19. Susa M, Oguro S, Kikuta K, et al. Novel MR imaging method–MAVRIC–for metal artifact suppression after joint replacement in musculoskeletal tumor patients. *BMC Musculoskelet Disord*. 2015;16:377.
20. Mackowiak PA, Jones SR, Smith JW. Diagnostic value of sinus-tract cultures in chronic osteomyelitis. *JAMA*. 1978;239:2772–2775.
21. Bernard L, Uçkay I, Vuagnat A, et al. Two consecutive deep sinus tract cultures predict the pathogen of osteomyelitis. *Int J Infect Dis*. 2010;14:e390–e393.
22. Harik NS, Smeltzer MS. Management of acute hematogenous osteomyelitis in children. *Expert Rev Anti Infect Ther*. 2010;8:175–181.
23. Bocchini CE, Hulten KG, Mason EO Jr, et al. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. *Pediatrics*. 2006;117:433–440.
24. Key JA. The classic: sulfonamides in the treatment of chronic osteomyelitis. 1944. *Clin Orthop Relat Res*. 2009;467:1662–1669.
25. Tice AD, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. *Am J Med*. 2003;114:723–728.
26. Paladino JA, Poretz D. Outpatient parenteral antimicrobial therapy today. *Clin Infect Dis*. 2010;51(suppl 2):S198–S208.
27. Rao SN, Rhodes NJ, Lee BJ, et al. Treatment outcomes with cefazolin versus oxacillin for deep-seated methicillin-susceptible *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother*. 2015;59: 5232–5238.
28. Youngster I, Shenoy ES, Hooper DC, et al. Comparative evaluation of the tolerability of cefazolin and nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* infections in the outpatient setting. *Clin Infect Dis*. 2014;59:369–375.
29. Wieland BW, Marcantoni JR, Bommarito KM, et al. A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin-susceptible *Staphylococcus aureus*. *Clin Infect Dis*. 2012;54:585–590.
30. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285–292.
31. Vuagnat A, Stern R, Lotthe A, et al. High dose vancomycin for osteomyelitis: continuous vs. intermittent infusion. *J Clin Pharm Ther*. 2004;29:351–357.
32. Jeffres MN. The whole price of vancomycin: toxicities, troughs, and time. *Drugs*. 2017;77:1143–1154.
33. Rayner CR, Baddour LM, Birmingham MC, et al. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. *Infection*. 2004;32:8–14.
34. Soriano A, Miro O, Mensa J. Mitochondrial toxicity associated with linezolid. *N Engl J Med*. 2005;353: 2305–2306.
35. Cattaneo D, Orlando G, Cozzi V, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. *Int J Antimicrob Agents*. 2013;41:586–589.
36. Moenster RP, Linneman TW, Call WB, et al. The potential role of newer gram-positive antibiotics in the setting of osteomyelitis of adults. *J Clin Pharm Ther*. 2013;38:89–96.
37. Ashizawa N, Tsuji Y, Kawago K, et al. Successful treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis with combination therapy using linezolid and rifampicin under therapeutic drug monitoring. *J Infect Chemother*. 2016;22:331–334.
38. Seaton RA, Malizos KN, Viale P, et al. Daptomycin use in patients with osteomyelitis: a preliminary report from the EU-CORESM database. *J Antimicrob Chemother*. 2013;68:1642–1649.
39. Malizos K, Sarma J, Seaton RA, et al. Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry. *Eur J Clin Microbiol Infect Dis*. 2016;35:111–118.
40. Hagiya H, Haruki Y, Uchida T, et al. Emergence of daptomycin-resistant *Staphylococcus aureus* during treatment. *Intern Med*. 2016;55:73–78.
41. Euba G, Murillo O, Fernández-Sabé N, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. *Antimicrob Agents Chemother*. 2009;53:2672–2676.
42. Curis E, Pestre V, Jullien V, et al. Pharmacokinetic variability of clindamycin and influence of rifampicin on clindamycin concentration in patients with bone and joint infections. *Infection*. 2015;43:473–481.
43. Bernard A, Kermarrec G, Parize P, et al. Dramatic reduction of clindamycin serum concentration in staphylococcal osteoarticular infection patients treated with the oral clindamycin-rifampicin combination. *J Infect*. 2015;71:200–206.
44. Lalikian K, Parsiani R, Won R, et al. Ceftaroline for the treatment of osteomyelitis caused by methicillin-resistant *Staphylococcus aureus*: a case series. *J Chemother*. 2017;1–5.
45. Turner RB, Wilson DE, Saedi-Kwon H, et al. Comparative analysis of neutropenia in patients receiving prolonged treatment with ceftaroline. *J Antimicrob Chemother*. 2017.
46. Harting J, Fernandez F, Kelley R, et al. Telavancin for the treatment of methicillin-resistant *Staphylococcus aureus* bone and joint infections. *Diagn Microbiol Infect Dis*. 2017;89:294–299.
47. Schroeder CP, Van Anglen LJ, Dretler RH, et al. Outpatient treatment of osteomyelitis with telavancin. *Int J Antimicrob Agents*. 2017;50:93–96.
48. Chuan J, Zhang Y, He X, et al. Systematic review and meta-analysis of the efficacy and safety of telavancin for treatment of infectious disease: are we clearer? *Front Pharmacol*. 2016;7:330.
49. Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences and lessons to be drawn. *Expert Opin Pharmacother*. 2013;14:723–734.
50. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.
51. Williams DN, Rehm SJ, Tice AD, et al. Practice guidelines for community-based parenteral anti-infective therapy. ISDA Practice Guidelines Committee. *Clin Infect Dis*. 1997;25:787–801.
52. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. *PM R*. 2009;1:471–489.
53. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. *Clin Infect Dis*. 2006;43:193–198.
54. Kranke P, Bennett M, Roeckl-Wiedmann I, et al. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2004;(2):CD004123.
55. Burns TC, Stinner DJ, Mack AW, et al. Microbiology and injury characteristics in severe open tibia fractures from combat. *J Trauma Acute Care Surg*. 2012;72:1062–1067.
56. DeLong WG Jr, Born CT, Wei SY, et al. Aggressive treatment of 119 open fracture wounds. *J Trauma*. 1999;46:1049–1054.
57. Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg Br*. 1995;77:93–97.
58. Hutson JJ Jr, Dayicioglu D, Oeltjen JC, et al. The treatment of Gustilo grade IIIB tibia fractures with application of antibiotic spacer, flap, and sequential distraction osteogenesis. *Ann Plast Surg*. 2010;64:541–552.
59. Stannard JP, Volgas DA, Stewart R, et al. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma*. 2009;23:552–557.
60. Kindsfater K, Jonassen EA. Osteomyelitis in grade II and III open tibia fractures with late débridement. *J Orthop Trauma*. 1995;9:121–127.
61. Schenker ML, Yannascoli S, Baldwin KD, et al. Does timing to operative débridement affect infectious complications in open long-bone fractures? A systematic review. *J Bone Joint Surg Am*. 2012;94:1057–1064.
62. Patzakis MJ, Wilkins J, Moore TM. Use of antibiotics in open tibial fractures. *Clin Orthop Relat Res*. 1983;178:31–35.
63. Dellinger EP, Caplan ES, Weaver LD, et al. Duration of preventive antibiotic administration for open extremity fractures. *Arch Surg*. 1988;123:333–339.
64. Hauser CJ, Adams CA Jr, Eachempati SR. Surgical Infection Society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. *Surg Infect (Larchmt)*. 2006;7:379–405.
65. Saveli CC, Morgan SJ, Belknap RW, et al. Prophylactic antibiotics in open fractures: a pilot randomized clinical safety study. *J Orthop Trauma*. 2013;27:552–557.
66. Lloyd BA, Murray CK, Shaikh F, et al. Early infectious outcomes after addition of fluoroquinolone or aminoglycoside to posttrauma antibiotic prophylaxis in combat-related open fracture injuries. *J Trauma Acute Care Surg*. 2017;83:854–861.
67. Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg Br*. 1995;77:93–97.
68. Zalavras CG, Patzakis MJ, Holtom P. Local antibiotic therapy in the treatment of open fractures and osteomyelitis. *Clin Orthop Relat Res*. 2004;427:86–93.
69. Zimmerli W, Widmer AF, Blatter M, et al. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. *JAMA*. 1998;279:1537–1541.
70. Trampuz A, Widmer AF. Infections associated with orthopedic implants. *Curr Opin Infect Dis*. 2006;19: 349–356.
71. Nguyen S, Pasquet A, Legout L, et al. Efficacy and tolerance of rifampicin-linezolid compared with rifampicin-cotrimoxazole combinations in prolonged oral therapy for bone and joint infections. *Clin Microbiol Infect*. 2009;15:1163–1169.
72. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022–1029.
73. Fantoni M, Trecarichi EM, Rossi B, et al. Epidemiological and clinical features of pyogenic spondylodiscitis. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):2–7.
74. Weissman S, Parker RD, Siddiqui W, et al. Vertebral osteomyelitis: retrospective review of 11 years experience. *Scand J Infect Dis*. 2014;46:193–199.
75. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis*. 2002;34:1342–1350.
76. Schnöring M, Brock M. [Prophylactic antibiotics in lumbar disc surgery: analysis of 1,030 procedures]. *Zentralbl Neurochir*. 2003;64:24–29.
77. Mete B, Kurt C, Yilmaz MH, et al. Vertebral osteomyelitis: eight years' experience of 100 cases. *Rheumatol Int*. 2012;32:3591–3597.
78. Solís García del Pozo J, Vives Soto M, Martínez Alfaro E, et al. [Vertebral osteomyelitis: description of a series of 103 cases and identification of predictive variables of the etiological group]. *Rev Clin Esp*. 2007;207:16–20.

79. Cone LA, Byrd RG, Potts BE, et al. Diagnosis and treatment of *Candida* vertebral osteomyelitis: clinical experience with a short course therapy of amphotericin B lipid complex. *Surg Neurol*. 2004;62:234–237, discussion 237.
80. Graham SM, Fishlock A, Millner P, et al. The management of gram-negative bacterial haematogenous vertebral osteomyelitis: a case series of diagnosis, treatment and therapeutic outcomes. *Eur Spine J*. 2013;22:1845–1853.
81. Kim CJ, Kim UJ, Kim HB, et al. Vertebral osteomyelitis caused by non-tuberculous mycobacteria: predisposing conditions and clinical characteristics of six cases and a review of 63 cases in the literature. *Infect Dis (Lond)*. 2016;48:509–516.
82. Akiyama T, Chikuda H, Yasunaga H, et al. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. *BMJ Open*. 2013;25:3. pii:e002412.
83. Vlahakis NE, Temesgen Z, Berbari EF, et al. Osteoarticular infection complicating enterococcal endocarditis. *Mayo Clin Proc*. 2003;78:623–628.
84. Hopkinson N, Stevenson J, Benjamin S. A case ascertainment study of septic discitis: clinical, microbiological and radiological features. *QJM*. 2001;94:465–470.
85. Hadjipavlou AG, Cesani-Vazquez F, Villaneuva-Meyer J, et al. The effectiveness of gallium citrate Ga 67 radionuclide imaging in vertebral osteomyelitis revisited. *Am J Orthop*. 1998;27:179–183.
86. Treglia G, Focacci C, Caldarella C, et al. The role of nuclear medicine in the diagnosis of spondylodiscitis. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):20–25.
87. Wenter V, Müller JP, Albert NL, et al. The diagnostic value of [(18)F]FDG PET for the detection of chronic osteomyelitis and implant-associated infection. *Eur J Nucl Med Mol Imaging*. 2016;43:749–761.
88. Kouijzer IJE, Scheper H, de Rooy JWJ, et al. The diagnostic value of (18)F-FDG-PET/CT and MRI in suspected vertebral osteomyelitis - a prospective study. *Eur J Nucl Med Mol Imaging*. 2017.
89. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61:e26–e46.
90. Corrah TW, Enoch DA, Aliyu SH, et al. Bacteraemia and subsequent vertebral osteomyelitis: a retrospective review of 125 patients. *QJM*. 2011;104:201–207.
91. Desoutter S, Cottier JP, Ghout I, et al. Susceptibility pattern of microorganisms isolated by percutaneous needle biopsy in nonbacteremic pyogenic vertebral osteomyelitis. *Antimicrob Agents Chemother*. 2015;59:7700–7706.
92. Chang CY, Simeone FJ, Nelson SB, et al. Is biopsying the paravertebral soft tissue as effective as biopsying the disk or vertebral endplate? 10-year retrospective review of CT-guided biopsy of diskitis-osteomyelitis. *AJR Am J Roentgenol*. 2015;205:123–129.
93. Kim BJ, Lee JW, Kim SJ, et al. Diagnostic yield of fluoroscopy-guided biopsy for infectious spondylitis. *AJNR Am J Neuroradiol*. 2013;34:233–238.
94. Hassoun A, Taur Y, Singer C. Evaluation of thin needle aspiration biopsy in the diagnosis and management of vertebral osteomyelitis (VO). *Int J Infect Dis*. 2006;10:486–487.
95. Gras G, Buzele R, Parienti JJ, et al. Microbiological diagnosis of vertebral osteomyelitis: relevance of second percutaneous biopsy following initial negative biopsy and limited yield of post-biopsy blood cultures. *Eur J Clin Microbiol Infect Dis*. 2014;33:371–375.
96. Yang SC, Fu TS, Chen LH, et al. Percutaneous endoscopic discectomy and drainage for infectious spondylitis. *Int Orthop*. 2007;31:367–373.
97. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet*. 2015;385: 875–882.
98. Park KH, Cho OH, Lee JH, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. *Clin Infect Dis*. 2016;62:1262–1269.
99. Carragee EJ, Kim D, van der Vlugt T, et al. The clinical use of erythrocyte sedimentation rate in pyogenic vertebral osteomyelitis. *Spine*. 1997;22:2089–2093.
100. Gupta A, Kowalski TJ, Osmon DR, et al. Long-term outcome of pyogenic vertebral osteomyelitis: a cohort study of 260 patients. *Open Forum Infect Dis*. 2014;1:ofu107.
101. Kowalski TJ, Berbari EF, Huddleston PM, et al. Do follow-up imaging examinations provide useful prognostic information in patients with spine infection? *Clin Infect Dis*. 2006;43:172–179.
102. Kowalski TJ, Berbari EF, Huddleston PM, et al. The management and outcome of spinal implant infections: contemporary retrospective cohort study. *Clin Infect Dis*. 2007;44:913–920.
103. Henke PK, Blackburn SA, Wainess RW, et al. Osteomyelitis of the foot and toe in adults is a surgical disease: conservative management worsens lower extremity salvage. *Ann Surg*. 2005;241:885–892.
104. Honda H, McDonald JR. Current recommendations in the management of osteomyelitis of the hand and wrist. *J Hand Surg Am*. 2009;34:1135–1136.
105. Rice JB, Desai U, Cummings AK, et al. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014;37:651–658.
106. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999;22:382–387.
107. Dargis V, Pantelejeva O, Jonushaite A, et al. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. *Diabetes Care*. 1999;22:1428–1431.
108. Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA*. 2008;299:806–813.
109. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis*. 2008;47:519–527.
110. Senneville E, Morant H, Descamps D, et al. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. *Clin Infect Dis*. 2009;48: 888–893.
111. Gontcharova V, Youn E, Sun Y, et al. A comparison of bacterial composition in diabetic ulcers and contralateral intact skin. *Open Microbiol J*. 2010;4:8–19.
112. van Asten SA, La Fontaine J, Peters EJ, et al. The microbiome of diabetic foot osteomyelitis. *Eur J Clin Microbiol Infect Dis*. 2016;35:293–298.
113. Smith EM, Khan MA, Reingold A, et al. Group B streptococcus infections of soft tissue and bone in California adults, 1995-2012. *Epidemiol Infect*. 2015;143:3343–3350.
114. Brunel AS, Lamy B, Cyteval C, et al. Diagnosing pelvic osteomyelitis beneath pressure ulcers in spinal cord injured patients: a prospective study. *Clin Microbiol Infect*. 2016;22:267.e1–267.e8.
115. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care*. 2015;38:302–307.
116. Lipsky BA, Itani K, Norden C. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/ amoxicillin-clavulanate. *Clin Infect Dis*. 2004;38:17–24.
117. Copley LA, Kinsler MA, Gheen T, et al. The impact of evidence-based clinical practice guidelines applied by a multidisciplinary team for the care of children with osteomyelitis. *J Bone Joint Surg Am*. 2013;95:686–693.
118. Bouchoucha S, Drissi G, Trifa M, et al. [Epidemiology of acute hematogenous osteomyelitis in children: a prospective study over a 32 months period]. *Tunis Med*. 2012;90:473–478.
119. Bouchoucha S, Gafsi K, Trifa M, et al. [Intravenous antibiotic therapy for acute hematogenous osteomyelitis in children: short versus long course.]. *Arch Pediatr*. 2013;20:464–469.
120. Kaplan SL. Osteomyelitis in children. *Infect Dis Clin North Am*. 2005;19:787–797, vii.
121. Peltola H, Pääkönen M. Acute osteomyelitis in children. *N Engl J Med*. 2014;370:352–360.
122. Calvo C, Nunez E, Camacho M, et al. Epidemiology and management of acute, uncomplicated septic arthritis and osteomyelitis: Spanish Multicenter Study. *Pediatr Infect Dis J*. 2016;35:1288–1293.
123. Olarte L, Romero J, Barson W, et al. Osteoarticular infections caused by *Streptococcus pneumoniae* in children in the post-pneumococcal conjugate vaccine era. *Pediatr Infect Dis J*. 2017;36:1201–1204.
124. Peltola H, Pääkkönen M, Kallio P, et al. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J*. 2010;29:1123–1128.
125. García-País MJ, Rabuñal R, Armesto V, et al. *Streptococcus bovis* septic arthritis and osteomyelitis: a report of 21 cases and a literature review. *Semin Arthritis Rheum*. 2016;45:738–746.
126. Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for post discharge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169:120–128.
127. Giedion A, Holthusen W, Masel LF, et al. [Subacute and chronic "symmetrical" osteomyelitis]. *Ann Radiol (Paris)*. 1972;15:329–342.
128. Kundu BK, Naik AK, Bhargava S, et al. Diagnosing the SAPHO syndrome: a report of three cases and review of the literature. *Clin Rheumatol*. 2013;32:1237–1243.
129. Beretta-Piccoli BC, Sauvain MJ, Gal I, et al. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature. *Eur J Pediatr*. 2000;159:594–601.
130. Assmann G, Kueck O, Kirchhoff T, et al. Efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation: an interventional study. *Arthritis Res Ther*. 2009;11:R140.
131. Hatano H, Shigeishi H, Higashikawa K, et al. A case of SAPHO syndrome with diffuse sclerosing osteomyelitis of the mandible treated successfully with prednisolone and bisphosphonate. *J Oral Maxillofac Surg*. 2012;70:626–631.
132. Tlougan BE, Podjasek JO, O'Haver J, et al. Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with associated neutrophilic dermatoses: a report of seven cases and review of the literature. *Pediatr Dermatol*. 2009;26:497–505.
133. Takeuchi K, Matsusita M, Takagishi K. A case of SAPHO (synovitis-acne-pustulosis-hyperostosis-osteomyelitis) syndrome in which [18F]fluorodeoxyglucose positron emission tomography was useful for differentiating from multiple metastatic bone tumors. *Mod Rheumatol*. 2007;17:67–71.
134. Roldán JC, Terheyden H, Dunsche A, et al. Acne with chronic recurrent multifocal osteomyelitis involving the mandible as part of the SAPHO syndrome: case report. *Br J Oral Maxillofac Surg*. 2001;39:141–144.
135. Adeyemi O, Sokkary N, Dietrich J. Pubic osteomyelitis resulting in rectovaginal fistula in an adolescent female. *J Pediatr Adolesc Gynecol*. 2013;26:e9–e11.
136. Choi H, McCartney M, Best TM. Treatment of osteitis pubis and osteomyelitis of the pubic symphysis in athletes: a systematic review. *Br J Sports Med*. 2011;45:57–64.
137. Dunk RA, Langhoff-Roos J. Osteomyelitis of the pubic symphysis after spontaneous vaginal delivery. *BMJ Case Rep*. 2010;pii:bcr0120102610.
138. Kroft J, Kung RC. Postoperative pubic symphysis osteomyelitis after laparoscopic two-team sling with anterior and posterior colporrhaphy. *J Minim Invasive Gynecol*. 2009;16:513–515.
139. Kim SB, Jung WK, Song DI, et al. Vesicocutaneous fistula presenting groin abscess and chronic osteomyelitis in pubic bone. *Clin Orthop Surg*. 2009;1:176–179.
140. Dovas S, Liakopoulos V, Simopoulou T, et al. A case report of osteomyelitis pubis in a hemodialysis patient with diabetes mellitus. *Ther Apher Dial*. 2008;12:409–412.
141. Gamble K, Dardarian TS, Finstein J, et al. Osteomyelitis of the pubic symphysis in pregnancy. *Obstet Gynecol*. 2006;107(2 Pt 2):477–481.
142. Madden-Fuentes RJ, Peterson AC. Pubic bone osteomyelitis and pubosymphyseal urinary fistula: a poorly recognized complication in prostate cancer survivors. *Oncology (Williston Park, NY)*. 2017;31:169–173.
143. Graham CW, Dmochowski RR, Faerber GJ, et al. Pubic osteomyelitis following bladder neck surgery using bone anchors: a report of 9 cases. *J Urol*. 2002;168:2055–2057, discussion 2057–2058.
144. Kammerer-Doak DN, Cornella JL, Magrina JF, et al. Osteitis pubis after Marshall-Marchetti-Krantz urethropexy: a pubic osteomyelitis. *Am J Obstet Gynecol*. 1998;179:586–590.
145. Yousef A, Pace A, Livesley P. Chronic haematogenous *Pseudomonas aeruginosa* osteomyelitis of the clavicle, a case report and review of the literature. *Eur J Pediatr*. 2006;165:424–426.
146. Burns P, Sheahan P, Doody J, et al. Clavicular osteomyelitis: a rare complication of head and neck cancer surgery. *Head Neck*. 2008;30:1124–1127.
147. Aggarwal AN, Dhammi IK, Singh AP, et al. Tubercular osteomyelitis of the clavicle: a report of four cases. *J Orthop Surg*. 2009;17:123–126.
148. Gerscovich EO, Greenspan A. Osteomyelitis of the clavicle: clinical, radiologic, and bacteriologic findings in ten patients. *Skeletal Radiol*. 1994;23:205–210.
149. Lewis SS, Sexton DJ. Metastatic complications of bloodstream infections in hemodialysis patients. *Semin Dial*. 2013;26:47–53.
150. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis*. 2010;14:e2–e12.
151. Neonato MG, Guilloud-Bataille M, Beauvais P, et al. Acute clinical events in 299 homozygous sickle cell

patients living in France. French Study Group on Sickle Cell Disease. *Eur J Haematol*. 2000;65:155–164.
152. Coulibaly Y, Keita M, Maiga AK, et al. [Osteomyelitis in sickle cell anemia patients in the Orthopedic and Trauma Department of the CHU Gabriel Toure]. *Mali Med*. 2010;25:29–31.
153. Berger E, Saunders N, Wang L, et al. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. *Arch Pediatr Adolesc Med*. 2009;163:251–255.
154. Skaggs DL, Kim SK, Greene NW, et al. Differentiation between bone infarction and acute osteomyelitis in children with sickle-cell disease with use of sequential radionuclide bone-marrow and bone scans. *J Bone Joint Surg Am*. 2001;83A:1810–1813.
155. Marti-Carvajal AJ, Agreda-Perez LH. Antibiotics for treating osteomyelitis in people with sickle cell disease. *Cochrane Database Syst Rev*. 2012;(12):CD007175.
156. Mikosch P. Miscellaneous non-inflammatory musculoskeletal conditions. Gaucher disease and bone. *Best Pract Res Clin Rheumatol*. 2011;25:665–681.
157. Kak V, Chandrasekar PH. Bone and joint infections in injection drug users. *Infect Dis Clin North Am*. 2002;16:681–695.
158. Williams DN, Rehm SJ, Tice AD, et al. Practice guidelines for community-based parenteral anti-infective therapy. ISDA Practice Guidelines Committee. *Clin Infect Dis*. 1997;25:787–801.
159. Shrestha NK, Shrestha J, Everett A, et al. Vascular access complications during outpatient parenteral antimicrobial therapy at home: a retrospective cohort study. *J Antimicrob Chemother*. 2016;71:506–512.
160. Trecarichi EM, Di Meco E, Mazzotta V, et al. Tuberculous spondylodiscitis: epidemiology, clinical features, treatment, and outcome. *Eur Rev Med Pharmacol Sci*. 2012;16(suppl 2):58–72.
161. Shikhare SN, Singh DR, Shimpi TR, et al. Tuberculous osteomyelitis and spondylodiscitis. *Semin Musculoskelet Radiol*. 2011;15:446–458.
162. Ikem IC, Bamgboye EA, Olasinde AA. Spinal tuberculosis: a 15 year review at OAUTHC Ile-Ife. *Niger Postgrad Med J*. 2001;8:22–25.
163. Batirel A, Erdem H, Sengoz G, et al. The course of spinal tuberculosis (Pott disease): results of the multinational, multicentre Backbone-2 study. *Clin Microbiol Infect*. 2015;21:1008.e9–1008.e18.
164. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
165. Sarria JC, Chutkan NB, Figueroa JE, et al. Atypical mycobacterial vertebral osteomyelitis: case report and review. *Clin Infect Dis*. 1998;26:503–505.
166. Villella A, Picard C, Jouanguy E, et al. Recurrent *Mycobacterium avium* osteomyelitis associated with a novel dominant interferon gamma receptor mutation. *Pediatrics*. 2001;107:E47.
167. Cruz AT, Antekeier SB. Chronic multifocal *Mycobacterium fortuitum* osteomyelitis following penetrating plantar trauma. *Am J Orthop*. 2012;41:E109–E111.
168. Sivan M, Bose D, Athanasou N, et al. *Mycobacterium marinum* osteomyelitis of a long bone. *Joint Bone Spine*. 2008;75:600–602.
169. Shimizu H, Mizuno Y, Nakamura I, et al. Vertebral osteomyelitis caused by non-tuberculous mycobacteria: case reports and review. *J Infect Chemother*. 2013;19:972–977.
170. Kulasegaram R, Richardson D, Macrae B, et al. *Mycobacterium xenopi* osteomyelitis in a patient on highly active antiretroviral therapy (HAART). *Int J STD AIDS*. 2001;12:404–406.
171. Vasireddy R, Vasireddy S, Brown-Elliott BA, et al. *Mycobacterium arupense, Mycobacterium heraklionense,* and a newly proposed species, "*Mycobacterium virginiense*" sp. nov., but not *Mycobacterium nonchromogenicum*, as species of the *Mycobacterium terrae* complex causing tenosynovitis and osteomyelitis. *J Clin Microbiol*. 2016;54:1340–1351.
172. Abu-Nader R, Terrell CL. *Mycobacterium bovis* vertebral osteomyelitis as a complication of intravesical BCG use. *Mayo Clin Proc*. 2002;77:393–397.
173. Jiang Z, Wang Y, Jiang Y, et al. Vertebral osteomyelitis and epidural abscess due to *Aspergillus nidulans* resulting in spinal cord compression: case report and literature review. *J Int Med Res*. 2013;41:502–510.
174. Zhang Y, Yu YS, Tang ZH, et al. Cryptococcal osteomyelitis of the scapula and rib in an immunocompetent patient. *Med Mycol*. 2012;50:751–755.
175. Gamaletsou MN, Kontoyiannis DP, Sipsas NV, et al. *Candida* osteomyelitis: analysis of 207 pediatric and adult cases (1970-2011). *Clin Infect Dis*. 2012;55:1338–1351.
176. Edupuganti S, Rouphael N, Mehta A, et al. *Fusarium falciforme* vertebral abscess and osteomyelitis: case report and molecular classification. *J Clin Microbiol*. 2011;49:2350–2353.
177. Waterman BR, Waterman SM, McCoy AC, et al. Coccidioidal osteomyelitis of the patella. *Orthopedics*. 2010;33:271–273.
178. McCabe MP, Heck RK. *Histoplasma* osteomyelitis simulating giant-cell tumor of the distal part of the radius: a case report. *J Bone Joint Surg Am*. 2010;92:708–714.
179. Shigemura T, Agematsu K, Yamazaki T, et al. Femoral osteomyelitis due to *Cladophialophora arxii* in a patient with chronic granulomatous disease. *Infection*. 2009;37:469–473.
180. Martirosyan NL, Skoch JM, Zaninovich O, et al. A paradigm for the evaluation and management of spinal coccidioidomycosis. *Surg Neurol Int*. 2015;6:107.
181. Taj-Aldeen SJ, Rammaert B, Gamaletsou M, et al. Osteoarticular infections caused by non-*Aspergillus* filamentous fungi in adult and pediatric patients: a systematic review. *Medicine (Baltimore)*. 2015;94:e2078.
182. von Eiff C, Bettin D, Proctor RA, et al. Recovery of small colony variants of *Staphylococcus aureus* following gentamicin bead placement for osteomyelitis. *Clin Infect Dis*. 1997;25:1250–1251.
183. La Scola B, Michel G, Raoult D. Use of amplification and sequencing of the 16S rRNA gene to diagnose *Mycoplasma pneumoniae* osteomyelitis in a patient with hypogammaglobulinemia. *Clin Infect Dis*. 1997;24:1161–1163.

105 Orthopedic Implant–Associated Infections

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SHORT VIEW SUMMARY

PERIPROSTHETIC JOINT INFECTION (PJI)

Diagnosis

- Determination that a prosthetic joint is infected depends on recovery of an organism from a joint aspirate or surgically obtained material from the joint, although inflammation, wound dehiscence, a draining sinus tract, joint effusion, and early loosening of the prosthesis can point toward this diagnosis.

Microbiology

- The most frequent microorganisms are *Staphylococcus aureus,* coagulase-negative staphylococci, and streptococci.
- *Cutibacterium* (formerly *Propionibacterium*) *acnes* is the most important microorganism in periprosthetic shoulder infection.
- Microorganisms establish a biofilm on the surface of the implant.

Pathogenesis

- Foreign devices are covered by host proteins (e.g., fibronectin) after implantation, favoring bacterial adherence.
- The minimal infecting dose is greater than 10,000-fold lower in the presence than in the absence of an implant.
- Granulocyte function around the implant is impaired (activation and degranulation).

Clinical Manifestations

- Acute exogenous PJI produces local signs of inflammation (wound dehiscence, secretion, erythema).
- Acute hematogenous PJI involves new-onset pain at any time after implantation, initially without local signs of infection, and new-onset articular effusion.
- In chronic PJI, pain occurs because of early loosening, local inflammation, sinus tract, and chronic articular effusion.

Treatment

- The cornerstone of successful treatment is early diagnosis.
- Cure is possible only with adequate surgery combined with appropriate antibiotic therapy.
- A treatment algorithm (see Fig. 105.1) allows one to choose the most appropriate surgical intervention: débridement with retention, one-stage exchange, two-stage exchange, removal without replacement, or suppressive therapy.
- Guidelines are available at www.idsociety.org/Organ_System/#Skeletal%20%28Bones%20&%20Joints%29.

INTERNAL FIXATION–ASSOCIATED INFECTION

Diagnosis

- Diagnosis of infection associated with implanted devices used to stabilize bone fractures, such as pins and rods, requires culture of the device, usually after surgical removal. Pain, inflammation, wound dehiscence, or loosening of the fixation device often indicates infection.

Microbiology

- Microbiology is comparable with that of PJI. Staphylococci are the most important pathogens.
- In open fractures, the wound is contaminated with environmental bacteria.

Pathogenesis

- The exogenous route plays a more important role than the hematogenous route.
- Infection may also occur via an adjacent focus (contiguous).

Clinical Manifestations

- Acute early postoperative infections cause wound healing disturbances, discharge, and erythema.
- In the case of acute symptoms that occur after an uneventful postoperative period, if systemic infection signs are dominating, pain is the most important local sign. Other local features are absent in the beginning and become apparent in the course of disease.
- Acute symptoms may also be due to reactivation of chronic posttraumatic osteomyelitis that has been silent for many years: Pain may occur without prominent systemic inflammatory signs.
- Chronic symptoms include sinus tract, pain, and implant loosening.

Treatment

- Bone fractures are less susceptible to infection if stabilized.
- In acute infections, retain implant with débridement and antimicrobial therapy until the fracture is consolidated.
- In chronic infections, the implant must be removed. When delayed infections on implants are suppressed with antimicrobials, the hardware must be removed after healing of bone fracture.

Orthopedic devices are used to stabilize bone fractures, fuse the vertebral column, correct deformities such as scoliosis, and replace damaged joints.[1,2,3] Whereas internal stabilization devices could be removed after a bone fracture is healed, prosthetic joints are kept in the body as long as their function remains full and pain free. The presence of an implant increases the risk for an infection because its local susceptibility for bacterial adherence is high.[4] Thus, even with the most meticulous infection control, implant-associated infections occur. The optimal management of orthopedic implant–associated infections requires close cooperation of experienced specialists in infectious diseases, microbiology, orthopedic and trauma surgery, and plastic surgery.

PERIPROSTHETIC JOINT INFECTION

Definition

The classic Centers for Disease Control and Prevention definition of wound infection is not applicable for implant-associated infections,[5] because superficial and deep wound infection cannot reliably be differentiated clinically.[6] Therefore, even in the case of a presumably "superficial" wound infection, revision surgery must be considered. Empirical antibiotic treatment without diagnostic workup should be avoided in the absence of life-threatening sepsis.

The definition of periprosthetic joint infection (PJI) should have a high sensitivity, in order not to delay the diagnosis of PJI. Use of the modified Infectious Diseases Society of America (IDSA) criteria increases the sensitivity of the diagnosis (Table 105.1).[3,7–11] C-reactive protein (CRP) is not a sensitive parameter in patients with PJI caused by low-virulence microorganisms.[12] The detection of microorganisms in intraoperative specimens from synovial fluid, tissue, or bone cement fragments is important. Swabs from the operative site or from a draining sinus are difficult to interpret and are not recommended. According to Bémer and colleagues,[13] four perioperative samples seeded on three culture media were sufficient for diagnosing PJI. As a criterion for PJI,

TABLE 105.1 Definition of Periprosthetic Joint Infection (at Least One Criterion Required)

- Presence of a sinus tract communicating with the prosthetic joint.
- Presence of purulence without another known etiology surrounding the prosthetic device.
- Acute inflammation consistent with infection at histopathologic examination of periprosthetic tissue (>5 granulocytes per high-power field [HPF] as average in 10 HPFs).
- Elevated leukocyte count in the synovial fluid or predominance of neutrophils, or both.[14,15]
- Growth of identical microorganism in at least two intraoperative cultures or combination of preoperative aspiration and intraoperative cultures in case of a low-virulence microorganism (e.g., coagulase-negative staphylococci, *Cutibacterium acnes*). In case of a virulent microorganism (e.g., *Staphylococcus aureus, Escherichia coli*), growth in a single specimen from synovial fluid or periprosthetic tissue, or both, and/or sonication fluid may also represent periprosthetic joint infection. However, growth in a single specimen must always be considered in the context of other criteria, and the constellation of diagnostic procedures (e.g., previous antimicrobial treatment) must be taken into account.

detection of the same microorganisms in at least two samples is required. A single positive culture of a pathogen belonging to the skin microbiome (e.g., *Cutibacterium acnes,* coagulase-negative staphylococci) does not confirm PJI. There are criteria for PJI irrespective of proof of a pathogen, as shown in Table 105.1. These include an abscess or a sinus tract that communicates with the joint or the presence of purulence in the affected joint. Other criteria for PJI include an elevated leukocyte count or the predominance of neutrophils in the synovial fluid or both,[14,15] and acute inflammation consistent with infection at histopathologic examination of periprosthetic tissue.[16,17]

Pathogenesis

Prosthetic joints are made of metal and polymers, most commonly polyethylene inlay between metal shell and metal head. Bone cement (i.e., polymethyl methacrylate [PMMA]) is frequently employed at the metal-bone interface. Biocompatible materials do not cause inflammation in the absence of infection and are therefore selected for implantation.[18]

After implantation, the device is covered by host proteins (e.g., fibronectin) favoring bacterial adherence.[19] Complement in interstitial fluid can be activated at the surface of polymeric implants, such as polyethylene particles, which results in degranulation of local neutrophils.[4] In addition, it has been shown that granulocytes interact with the nonphagocytosable surface of implants. This process is called "frustrated phagocytosis" and results in impaired granulocyte function.[4,20,21] Implants and polymer particles, which are produced in variable amounts after arthroplasty, compromise granulocyte function.[22] This interaction with wear particles, fragments from within the joint space, results in an impaired granulocyte function and favors aseptic loosening of joint prostheses.[23]

Implanted foreign material is highly susceptible to local infection. In 1957, Elek and Conen[24] showed in human volunteers that in the vicinity of suture material, the minimal abscess-forming dose is as low as 100 colony-forming units (CFUs) of *Staphylococcus aureus,* which is more than 10,000-fold lower than in the absence of foreign material. This observation was reproduced in an animal model of foreign body–associated infection using different gram-positive and gram-negative microorganisms.[20,25,26,27,28] The route of infection can be exogenous, hematogenous, or contiguous spread. The last route is rare and implicates spread from an adjacent focus of infection (e.g., osteomyelitis, deep soft tissue infection). The animal model demonstrated that microorganisms can seed on an implant from a distant site by the hematogenous route.[29] Finally, the exogenous route includes a joint inoculation of microorganisms during surgery or in the early postoperative period. Exogenous infections can also occur later via a penetrating event (e.g., trauma, injection).

Implant-associated microorganisms growing as a biofilm are protected from phagocytosis.[30] In addition, most antibiotics do not kill adherent bacteria despite penetration into the biofilm.[31,32] The lack of efficacy of many antimicrobial agents depends on the low growth rate of organisms in the biofilm.[33] As an exception, rifampin can eliminate biofilm-associated gram-positive microorganisms,[25,34,35,36] and fluoroquinolones are active against biofilms from gram-negative bacilli.[27,28,37,38]

Classification

No classification system of PJI is unanimously accepted. On the basis of the two major infection routes, PJI can be classified as either exogenous or hematogenous infection.[39] In considering the virulence of bacteria and the host response of immunocompetent patients, PJI can be classified on the basis of symptoms as acute or chronic. The traditional classification differentiates among early (those developing within <3 months after implantation), delayed (3–24 months after surgery), and late (>24 months after implantation) infection.[3,7] In clinical practice, it is more useful to classify PJI as follows:

- Acute hematogenous PJI: Infection with 3 weeks' duration of symptoms or less after an uneventful postoperative period
- Early postinterventional PJI: Infection that manifests within 1 month after an invasive procedure (surgery or arthrocentesis)
- Chronic PJI: Infection with symptoms that persist for more than 3 weeks and are beyond the early postinterventional period

This simple classification allows the differentiation between PJI, which can be potentially cured with débridement and implant retention, and the infection that requires device removal for cure.[3,7] Acute hematogenous infection is generally caused by virulent bacteria, and débridement is required in order for the device to be retained. This type of PJI can occur at any time after surgery, as long as the implant is in the body.[40–44] Early postoperative PJI manifests with poor wound healing, joint fluid accumulation, or persisting pain. In these cases, early detection with a high degree of suspicion, rapid diagnostic workup, and prompt surgical treatment are required for retention of the implant. If these (exogenous) infections are not detected early after surgery (within the first month) or if symptoms persist for more than 3 weeks, or both, chronic PJI develops, irrespective of the infection route. This form of infection requires removal of all hardware and bone cement for cure.

Risk Factors

Several risk factors have been described for the development of PJI.[6,45–55] Most data are derived from patients with total hip and knee arthroplasties. Some of the proposed risk factors have to be interpreted with caution because the corresponding studies used different statistical methods or focused on only one particular anatomic site. Risk factors for acquiring PJI can be categorized as patient characteristics, surgery-related and postoperative factors, and risk during bacteremia.[55] Goltz and colleagues[56] showed that the individual risk for PJI can be reliably predicted by using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator (http://riskcalculator.facs.org/).

Patient Characteristics

Diabetes mellitus, obesity (body mass index ≥30 [weight in kg/height in m^2]), rheumatic diseases, and immunosuppressive therapy are among the most frequently reported risk factors for developing PJI. These factors influence wound healing and predispose to many infectious diseases. Congestive heart failure, chronic pulmonary disease, peripheral vascular disease, malignancy, coagulopathy, and preoperative anemia, among other comorbidities, have been described as risk factors for PJI. Preoperative asymptomatic bacteriuria is not a risk factor.[57,58] Overall, it is rather the "net state of polymorbidity" of a patient (e.g., number of comorbidities, physical status) than a single variable that plays a unique role in infection pathogenesis. Finally, the patient's history with respect to previous tissue damage should be considered. Previous joint surgery, mainly previous arthroplasty, has been identified as a risk factor.

Surgery-Related Risk Factors

The complexity and duration of the procedure increase the risk of the joint to become inoculated with microorganisms. A prolonged operative time and multiple simultaneous joint revisions are risk factors for acquiring PJI.

Postoperative Factors

In essence, all wound complications (e.g., delayed healing, drainage or persistent dehiscence, hematoma, seroma, wet wound after initially being dry) increase the risk for infection. Also, postoperative hyperglycemia is a risk factor.[45] Finally, there are risk factors for PJI that are primarily not associated with the surgical procedure or its wound healing. These include atrial fibrillation, myocardial infarction, and a prolonged hospital stay.

Risk During Bacteremia

Urinary tract infection in the postoperative period has been identified as a risk factor for PJI. The incidence of hematogenous seeding to a joint from a remote infection is, however, low (0.1%).[59] This is different for *S. aureus*. The rate of PJI after *S. aureus* bacteremia is approximately 35%.[41–43] This high infection rate indicates that patients with previously uninfected prosthetic joints and *S. aureus* bacteremia should be carefully monitored clinically for the development of PJI. Again, rapid diagnosis of PJI may avoid an exchange of the prosthesis because these infections can be cured with débridement and implant retention.

Microbiology

As a rule, all microorganisms can cause PJI, including mycobacteria.[60,61] However, staphylococci are the most commonly isolated microorganisms. In five studies with a total of 1130 episodes of PJI, the following microorganisms were detected.[6,62,63,64,65]

- *S. aureus,* 21% to 43%
- Coagulase-negative staphylococci, 17% to 39%
- Streptococci, 7% to 12%
- Gram-negative aerobic bacilli, 5% to 12%
- Enterococci, 1% to 8%
- Anaerobic bacteria, 2% to 6%

Other microorganisms such as diphtheroids and *Candida* spp. cause PJI less frequently.

C. acnes is responsible for about 3% of periprosthetic hip and knee infection but up to 38% of periprosthetic shoulder infection.[65,66] In about 15%, polymicrobial infection occurs.[67] Infections with mixed flora are mainly observed in patients with protracted wound healing, resulting in exogenous superinfection.[68] In 4% to 15% of cases, no microorganism is detected.[6,62–65,67,69] This proportion depends on the frequency of pretreatment with antimicrobial agents, type of microorganism, and microbiologic technique.

Clinical Manifestations and Differential Diagnosis

Acute Periprosthetic Joint Infection

The description of the clinical manifestation stems mainly from hip and knee PJI. However, PJI in other joints may manifest differently.[70] Acute exogenous infection typically causes local signs of inflammation, whereas acute hematogenous infection is characterized by new-onset pain, initially without prominent local signs of infection. Acute infections are usually caused by virulent pathogens, mainly *S. aureus,* β-hemolytic streptococci, and less frequently gram-negative bacilli.[3,71]

Most early (postoperative) acute infections have an exogenous origin. Wound dehiscence, drainage, and erythema are typical signs. A systemic inflammatory response syndrome may be missing.[3,39] The differential diagnosis of postoperative acute PJI includes wound complications such as hematoma or seroma. Because the clinical differentiation of superficial and deep wound infection is not reliable,[6] each suspicious wound needs a careful orthopedic evaluation (e.g., surgical exploration of the site) in order to establish or exclude PJI.[72] Consideration of this principle increases the fraction of patients who can be cured with débridement and implant retention.

Acute-onset PJI occurring beyond the postoperative period is generally of hematogenous origin (acute hematogenous PJI). In such infections, systemic signs of inflammation are prominent. The patient typically reports profound pain at the site of the implant, although soft tissue damage is less frequent and less obviously visible than in early exogenous PJI.[3,39] Consequently, the differential diagnosis of acute PJI after an uneventful postsurgical period is narrow. It includes crystal arthropathy, which can be detected with microscopic examination of the synovial fluid and biopsy samples.[73] Venous thrombosis and arterial emboli in vessels that are in close anatomic proximity to the joint can imitate clinical signs of PJI.

All patients with acute symptoms, irrespective of the interval between prosthesis implantation and clinical manifestation, require rapid diagnostic workup because the implant can potentially be retained if symptom duration is short.[3,7,72]

Chronic Periprosthetic Joint Infection

Chronic PJI can be exogenous or hematogenous. If the joint is infected at surgery by low-virulence organisms, infection often manifests beyond the early postoperative period (≥1 month). When symptoms persist for several weeks, irrespective of infection route, the PJI becomes chronic. The key symptoms are chronic joint effusion, pain caused by local inflammation or implant loosening, and, occasionally, sinus tracts. In addition, CRP and erythrocyte sedimentation rate (ESR) do not normalize after surgery and typically fluctuate within a slightly elevated range. However, these tests are not specific. The differential diagnosis includes mechanical failure, excessive wear debris, or allergy to the implant material.[74,75] The sensitivity of CRP is limited in patients with low-virulence microorganisms. It has been shown to be normal (<8 mg/L) in 32% of patients with documented chronic PJI.[12] If early loosening is caused by mechanical failure, one-stage exchange is appropriate, whereas in patients with septic loosening the surgical strategy depends on the infecting agent.[76] Thus, it is crucial to identify PJI cases before definitive surgery. The consequence of missing a low-grade infection is an inadequate revision arthroplasty and subsequent failure. In view of the generally long-lasting course in chronic PJI, there is sufficient time for thorough diagnostic procedures.

Diagnostic Procedures

Blood Tests

Leukocyte counts are diagnostically not helpful owing to poor sensitivity and low predictive values.[77] CRP and ESR are routinely used in the diagnostic workup of PJI. Both tests have good sensitivity but poor specificity. With a threshold at greater than or equal to 30 mm/h (ESR) and at greater than or equal to 10 mg/L (CRP), the sensitivities are 91% to 97% and the specificities are 70% to 78%.[8,77,78] Thus, both tests can be used to estimate the likelihood of a PJI with negative predictive values of about 96%. Sensitivity is less for low-virulence organisms, such as *C. acnes.*[12,79,80] Procalcitonin (PCT), which is a promising biomarker in patients with respiratory tract infections, has not proved helpful in differentiating septic from aseptic loosening.[81,82] In addition, postoperative serum PCT levels are rarely elevated in patients with PJI without sepsis syndrome.[83] In contrast, interleukin-6 (IL-6) values above the cutoff value of 10 pg/L appear to have an excellent sensitivity of nearly 100% to predict the presence of PJI.[77,81] However, this test is not generally available and is costly.

Synovial Fluid Cell Counts

The threshold of leukocyte counts in synovial fluid for the diagnosis of PJI is much lower than for septic native joint arthritis. Published cutoff values show a sensitivity and specificity of about 90%. Because of differences in counting methods (automated versus manual) and interlaboratory variations in counting results, there is no uniformly accepted precise cutoff value. In hip arthroplasty, Schinsky and colleagues[15] reported optimal cutoff values of more than 4200 leukocytes per microliter, neutrophil fraction greater than 80%, or both. In patients with periprosthetic knee infection, Trampuz and colleagues[14] defined an optimal cutoff value of more than 1700 leukocytes per microliter, neutrophil fraction greater than 65%, or both. Similar results were shown by Ghanem and colleagues[84] for periprosthetic knee infection (more than 1100 leukocytes per microliter, >64% neutrophil fraction, or both). In these studies, patients with rheumatoid arthritis or joint hemorrhage, or those in the early postoperative period, were excluded. However, similar cutoff values were reported in synovial fluid of patients with and without inflammatory arthritis in periprosthetic hip infection, namely 3450 leukocytes per microliter versus 3444 leukocytes per microliter, and 78% and 75% neutrophil fraction, respectively.[85] In synovial fluid drawn shortly after surgery, the proposed cutoff values are much higher, namely,

more than 25,000 leukocytes per microliter.[86] In summary, leukocyte and differential counts are key parameters for the diagnosis of PJI, especially in patients with negative culture.

Synovial Fluid Culture

Conventional microbiologic cultures of synovial fluid have a moderate sensitivity of approximately 85% but an excellent specificity of greater than 95%.[78] However, published results often do not stratify whether the fluid was obtained by puncture, arthroscopy, or open surgery. A negative culture result does not exclude PJI. The sample sensitivity can be improved by use of polymerase chain reaction (PCR)[87] or by culturing synovial fluid in blood culture flasks.[88]

Intraoperative Samples for Culture and Histopathology

Swab cultures clearly have a lower sensitivity than cultures from periprosthetic tissue and synovial fluid, and must therefore not be used.[88] Culturing synovial fluid and periprosthetic tissue has the best accuracy, specificity, and sensitivity.[78] For the diagnosis of PJI, at least three specimens should be obtained.[7,89] The greatest accuracy is observed with four specimens processed with conventional culture and with three specimens cultured in blood culture bottles.[13,90,91]

Biopsy culture of *C. acnes* requires anaerobic conditions. Incubation time depends on multiple factors (e.g., time from sampling to laboratory, material preparation, culture media, incubation techniques), and hence may vary among institutions. Recent investigations have reported an incubation time of up to 10 days.[92,93]

Histopathologic specimens are difficult to interpret because the threshold of neutrophils per high-power field (HPF) varies among different experts, ranging from an average of 1 or more to 10 or more neutrophils when counting 10 HPFs. Many experts accept 5 or more neutrophils per HPF in ×40 magnification as a positive indicator for PJI.[17] Frozen sections can be used only in centers with experienced pathologists who are able to differentiate between mechanical failure and infection. This technique informs the surgeon in the operating room whether infection can be excluded, and therefore whether the planned one-stage exchange for early loosening can be performed.[94] In cases of chronic PJI, we recommend paraffin sections, which have been reported to be superior to frozen sections. If possible, each tissue sample should be cut into two pieces, labeled with their precise origin, and submitted one each to microbiologic and histopathologic examination. If dividing tissue sample is not possible (e.g., bone biopsies), two samples from the same location should be obtained. The comparison between culture results and histopathologic findings helps to differentiate between contamination and infection.

Sonication

Sonication of foreign-body material, such as an implant or parts of it, followed by culturing or use of molecular methods on the sonicate fluid, or both, allows detection of microorganisms in biofilms.[95] In a population with either PJI or aseptic failure, Trampuz and colleagues[96] performed a prospective trial comparing culture results from synovial fluid, periprosthetic tissue, and sonicate fluid. In this trial, the sensitivities for detecting PJI with the three different methods were 56.3%, 60.8%, and 78.5%, respectively, with specificities greater than 98%. According to a meta-analysis of 13 studies, the sensitivity of sonication culture is significantly better than that of traditional culture.[97,98] Improved sensitivity has also been reported when sonication of synovial fluid preceded PCR.[99]

Novel Diagnostic Procedures

α-Defensin Test

A quantitative and a qualitative immunoassay for α-defensin in joint fluid is commercially available (Synovasure; CD Diagnostics, Claymont, DE). α-Defensin is an antimicrobial peptide that is released by neutrophils and natural killer cells in response to inflammation. The assay has been reported to assist in the diagnosis of PJI, although its usefulness is controversial.[100,101,102] The result is not influenced by prior antibiotics, but metallosis is a potential source of false-positive results.[103,104] The necessity of sending the sample to the company for testing and the cost will be factored into the decision to use the test. In two recent studies, a lateral flow assay for rapid detection of α-defensin in synovial fluid had a limited sensitivity of 67% and 69%, respectively.[105,106] In addition, it has been shown that the sensitivity of leukocyte count is higher than that of the qualitative α-defensin test (86% vs. 54%; $P < .001$).[107] A strip test for detecting leukocyte esterase has also been used intraoperatively but has low sensitivity and gives false-positive results in bloody specimens.[108]

Molecular Diagnostics

Molecular methods have been used in synovial fluid, periprosthetic tissue specimens, and sonicate fluid from explanted prostheses or modular parts of them. Different techniques have been used, either broad-range PCR or specific multiplex PCR.[97,109,110] In patients pretreated with antibiotics, the sensitivity of broad-spectrum PCR is higher than that of culture, but still only about 70%.[87] In addition, it does not give information about the susceptibility of the microorganism with a few exceptions (e.g., *mecA* gene for methicillin resistance, *rpoB* gene for rifampin resistance). Thus it is mainly useful in combination with conventional cultures in pretreated patients. Use of specific PCR primers is potentially more sensitive for detecting defined microorganisms.[111] However, in a recent study the sensitivity of a multiplex PCR in sonication fluid (Unyvero i60 [Curetis Cie, Holzgerlingen, Germany], designed for detection of PJI) was not better than that of sonicate culture (53% vs. 58%).[112]

Imaging Procedures

Radiographs have a low sensitivity and specificity for the diagnosis of PJI. Radiolucency, osteolysis, and migration are signs of not only infection but also aseptic loosening.[113] Hence, the diagnostic role of radiography is limited. Ultrasonography is helpful in cases with joint effusion that cannot be clinically diagnosed and where guidance for joint aspiration is necessary. Computed tomography (CT) allows detection of soft tissue infection (abscesses, sinus tracts), prosthetic loosening, and bone erosion. With the use of special techniques, metallic artifacts can be minimized. However, this technique is more often used to estimate the extent of an infection than to determine whether or not an infection is present. Imaging interference occurs in the vicinity of metal implants. The indication for magnetic resonance imaging (MRI) is similar to that for CT.

With radionuclide imaging, signs of infection are visible before anatomic changes. The three-phase bone scan using a bone-seeking tracer (e.g., technetium 99m–labeled methylene diphosphonate [^{99m}Tc-MDP]) is sensitive for detecting infection but has poor specificity.[114] Bone remodeling and hence marker uptake is increased for at least 1 year after implantation.[115] Furthermore, heterotopic ossification and aseptic loosening also increase tracer uptake. The specificity can be improved to 80% to 90% with use of a more specific radiotracer such as ^{99m}Tc-ciprofloxacin (Infecton) or ^{99m}Tc–antigranulocyte monoclonal antibodies.[116,117] The use of labeled leukocytes is cumbersome and depends on the quality of the purification and labeling.[118] Unfortunately, the spatial resolution of nuclear scanning techniques is limited. Single-photon emission computed tomography plus conventional CT (SPECT-CT), which is performed with an integrated hybrid machine, offers a more precise localization of the radiotracer and should therefore be preferred. This method is mainly used with ^{99m}Tc-MDP, labeled leukocytes, or labeled antigranulocyte monoclonal antibodies. It improves the sensitivity and specificity as compared with the planar image. In 31 consecutive patients with suspected low-grade PJI, sensitivity, specificity, and accuracy improved from 66%, 60%, and 61%, respectively, to 89%, 73%, and 77%, respectively. The prevalence of PJI in this population was 29%.[119]

Positron Emission Tomography

Positron emission tomography (PET) examination plays an important role in the detection of malignant tumors. ^{18}F-fluorodeoxyglucose (FDG) accumulates in cells such as neutrophils and is intracellularly phosphorylated to a stable molecule. Therefore accumulation occurs in not only tumors but also inflammatory foci. According to a systematic review of 11 studies, including a total sample size of 635 prostheses, FDG-PET has good sensitivity (84.6%; 95% confidence interval [CI], 71%–93%) and specificity (84%; 95% CI, 68%–93%) for the detection of PJIs in

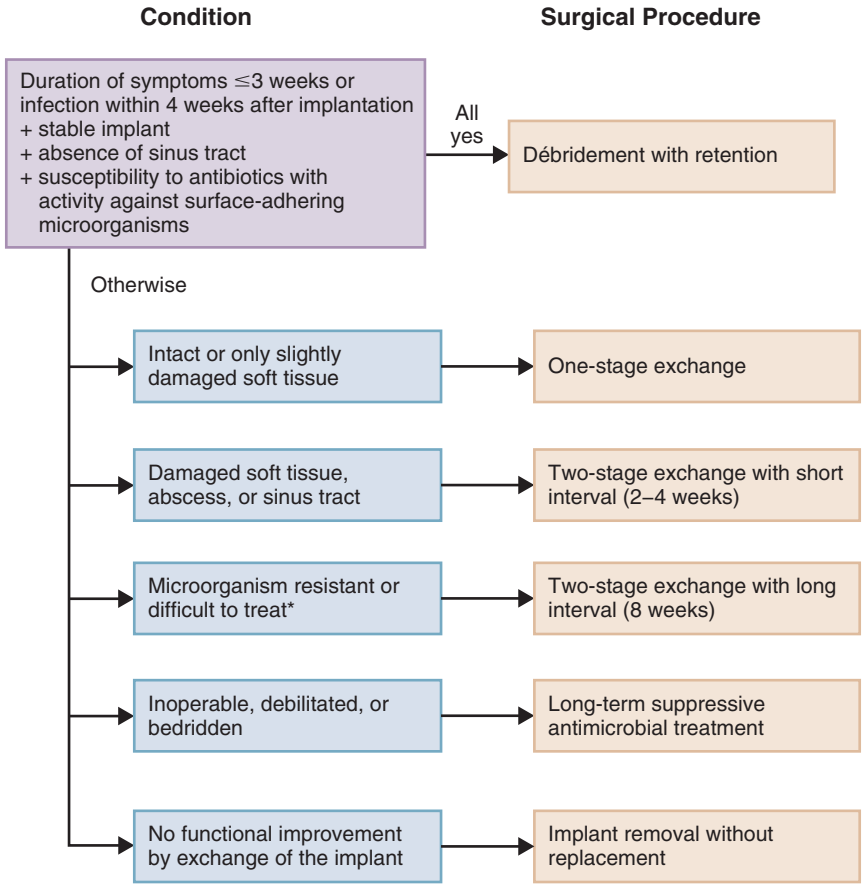

FIG. 105.1 Surgical treatment algorithm for prosthetic joint infections. *Difficult-to-treat microorganisms include microorganisms resistant to antibiotics with good oral bioavailability, rifampin-resistant staphylococci, and quinolone-resistant gram-negative bacilli and fungi. *(Modified from Trampuz A, Zimmerli W. Prosthetic joint infections: update in diagnosis and treatment.* Swiss Med Wkly. *2005;135:243–251.)*

hip and knee arthroplasties.[120] However, the individual studies show sensitivities between 22.2% and 100%, and specificities between 61.5% and 100%. Reasons for these inconsistent results are the nonspecific postoperative FDG uptake after total knee arthroplasty, the prolonged increased FDG uptake around the femoral neck, and the nonspecific FDG uptake around the distal part the prosthetic stem.[114,121] Thus PET cannot be recommended for routine clinical practice. In many countries costs are not covered for these novel imaging techniques.

Treatment Concepts

General Aspects

Cure at the first treatment attempt is crucial because with each treatment failure, tissue damage and functional integrity are worse. Delayed ambulation increases loss of muscle strength and increases chances of thromboembolism. Therefore, early referral to specialized centers is advised. As a rule, before starting treatment, it should be clear whether a curative or suppressive (palliative) approach will be taken. Cure is defined as a long-term pain-free functional joint with complete eradication of infection after a follow-up of 24 months following surgery. Eradication surgery requires a combination of both an appropriate surgical procedure and antimicrobial therapy. In contrast, palliative therapy is geared toward suppression of infection and thus of symptoms. In general, only minor or no surgery is performed with this strategy. Lifelong suppressive antimicrobial therapy may be necessary because the chance for cure is minimal.

The cornerstone of successful treatment is early diagnosis. The earlier the diagnosis, the less invasive is the surgical therapy. Accordingly, a high degree of suspicion is required and empirical antibiotic therapy without unequivocal diagnosis must be avoided.

Traditional standard treatment included two-stage exchange with meticulous removal of all necrotic tissue, bone cement, and the prosthesis combined with a prolonged course of antibiotics during the implant-free interval.[122] During the past 2 decades, an algorithm for the optimal surgical therapy of the different presentations was developed at our institute.[3,123] Choosing the least invasive treatment that cures infection is the most rational approach (Fig. 105.1). Because data from controlled trials comparing different surgical procedures are lacking, treatment concepts vary among different centers. Recommendations are therefore based on case series and expert opinions and published in the IDSA guidelines.[3,7,71,123] Considering the prerequisites for the successful use of each surgical procedure, all surgical interventions have a favorable outcome in more than 80% of the patients.[a]

Antimicrobial treatment without any surgical intervention is not curative but only suppressive. There are three different curative options: débridement and implant retention, one-stage exchange, and two-stage exchange. In addition, in special situations, microbiologic cure without restoration of full function can be reached with removal without replacement, arthrodesis, or amputation. There are some controversies among different specialized centers: (1) One-stage exchange is less commonly performed in the United States than it is in European centers; (2) in the case of two-stage exchange, the approach with a short interval is used in only a minority of centers; and (3) some centers continue suppressive antimicrobial therapy despite curative approach, considering the small uncertainty that the infection is not cured.[7,128] However, the benefit of stopping treatment (e.g., reducing side effects) outweighs that uncertainty. These controversial aspects will remain until controlled trials have been conducted. Fig. 105.1 shows a treatment algorithm that allows choosing the most appropriate surgical intervention based on several variables.[3,123] This algorithm has been developed for patients with hip and knee PJI.[3,62,63,129] In addition, it has also been implemented for shoulder and elbow prostheses.[66,130] In one review of shoulder

[a]References 3, 35, 36, 62, 63, 124, 125, 126, 127.

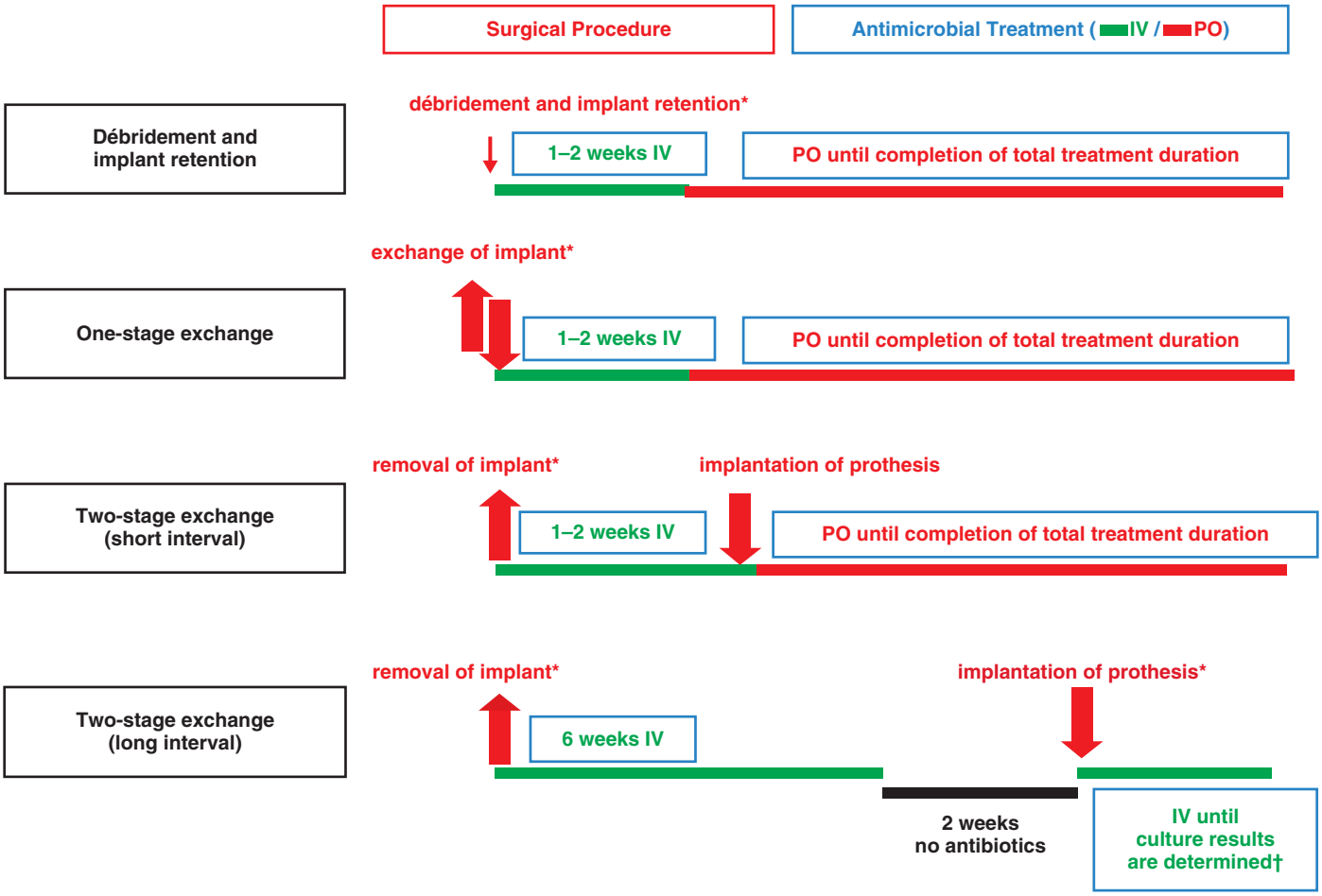

FIG. 105.2 Surgical intervention, route, and duration of antimicrobial therapy according to Zimmerli and colleagues.[3] *IV,* Intravenous route; PO, oral route; *, microbiologic sampling; †, continuation with the same antibiotic regimen. Samples are cultured for 10 to 14 days in most centers that are specialized for periprosthetic joint infection. If microbiologic results are confirmed to be negative, the antimicrobial treatment can be stopped.

periprosthetic infections, the rate of cure was 90% to 92% whether the implant was replaced in a one- or a two-stage procedure.[131] In contrast, the optimal surgical management of ankle PJI has not yet been defined.[70] In these patients, the surgical strategy is mainly dictated by the more difficult soft tissue situation. Fig. 105.2 shows the sequence of surgical interventions and the duration of intravenous and oral antimicrobial therapy.

Débridement With Retention of Implant

The success rate of this procedure is traditionally widely underestimated, because there are many published series with patients not qualifying to undergo it. However, the success rate is not lower than that of exchange surgery, provided that the following four conditions are fulfilled[b]:

- Acute infection (<3 weeks' duration of infectious symptoms or <1 month after implantation)
- Stable implant
- Pathogen susceptible to a biofilm-active antimicrobial agent (see later)
- No sinus tract and no periprosthetic abscess

The definition for duration of symptoms is based on a controlled trial.[36] Rapid and meticulous débridement of necrotic tissue is essential. In periprosthetic knee infection, the reported success rate is better after open surgery than after arthroscopic débridement (median reported success rates 86% vs. 56%).[133] In cases of open débridement, modular components should be exchanged, which results in reduction of the biofilm. The advantages of débridement with retention are the minimal invasive surgery and rapid rehabilitation.

[b]References 3, 7, 72, 124, 125, 132–135.

One-Stage Exchange

Direct exchange includes removal and reimplantation during the same surgical procedure. It can be chosen for patients with (1) a good soft tissue envelope and (2) a pathogen that is susceptible to oral antimicrobial agents with excellent bioavailability and activity on biofilms (see later). However, it is crucial to identify the causative pathogen before the surgical procedure. In general, effective antibiotic-impregnated bone cement is used.[136] However, cure rate with use of uncemented revision stems is excellent in infected total hip arthroplasties.[137]

Two-Stage Exchange

The two-stage exchange procedure starts with thorough removal of all necrotic tissue, bone cement, and all of the implant before reimplantation of a new device is performed at a second intervention.[127] After removal of all foreign material, an antibiotic-impregnated spacer, typically PMMA, is inserted in order to achieve some stability, allow some degree of mobility, prevent shrinking of the joint space, and produce a high local concentration of antibiotics. The need for local antibiotics in the spacer has never been proven in a comparative and prospective PJI trial. Interesting to note, in patients with a microorganism resistant to the antibiotic in the spacer, there is no measurable disadvantage regarding the outcome.[138] The advantage of staged exchange is the opportunity for removing all infected material before implantation of the new prosthesis. The disadvantage is the need for two surgical interventions, prolonged disability, and the interval with the biomechanically suboptimal spacer. Therefore, we favor a short interval of only 2 to 3 weeks before reimplantation, except in patients with difficult-to-treat microorganisms.[3] During the interval the bacterial load can be diminished and the soft tissue heals. This allows a treatment during one single hospitalization.

Antibiotics are not stopped before implantation, and no sampling is recommended during implantation. However, antibiotic treatment postoperatively is necessary, as in patients with débridement and retention or one-stage exchange. In patients with difficult-to-treat microorganisms (small-colony variants, rifampin-resistant staphylococci, fluoroquinolone-resistant gram-negative bacilli, fungi), early reimplantation should not be chosen.[3,139] The rationale for the long interval is the concept that difficult-to-treat microorganisms must be completely eradicated before reimplantation. These patients should be treated for 6 weeks. Because of potential adherence and persistence of these types of microorganisms on the spacer, we recommend a two-stage procedure with a spacerless interval.[139] Reimplantation should be delayed for 2 more weeks free of antibiotics in order to obtain reliable samples for microbiologic assessment. In these patients, the same antimicrobial treatment of the previous 6 weeks should be restarted after implantation of the new device. It can be definitely stopped when intraoperative culture results remain negative (see Fig. 105.2).

Antimicrobial Therapy

After microbiologic sampling, antimicrobial agents are administered by the intravenous route mainly for two reasons. First, the risk for emergence of resistance is highest during the initial phase, when the bacterial load is still high. Therefore, subinhibitory antimicrobial concentrations should be avoided. Second, enteral resorption may be compromised during the perioperative phase. Table 105.2 summarizes the pathogen-specific antimicrobial therapy, and Fig. 105.2 shows the timing of the intravenous and the oral therapy. It mainly depends on the type of surgery performed. The correct duration of treatment has never been tested in comparative studies. It is based on the reasoning that biofilm bacteria cannot be killed by host defense alone.[4] Therefore, PJI reoccurs if not all microorganisms are eliminated by débridement and antimicrobial therapy. For patients with implant retention, direct exchange, or two-stage exchange with a short interval, we propose a 3-month regimen. Some experts recommend 6 months for knee prostheses.[3,7] Several mainly observational studies, however, demonstrated

TABLE 105.2 Treatment of Implant-Associated Infections

MICROORGANISM	ANTIMICROBIAL AGENT[a]	DOSE	ROUTE
Staphylococcus spp.	Recommendation for the initial IV treatment phase (for 1–2 wk)		
Methicillin susceptible	Rifampin *plus*	450 mg q12h or 600 mg q24h[b]	PO/IV
	Nafcillin *or* oxacillin[c]	2 g q4h	IV
Methicillin resistant	Rifampin *plus*	450 mg q12h or 600 mg q24h[b]	PO/IV
	Vancomycin *or*	15 mg/kg q12h[d]	IV
	Daptomycin	8–10 mg/kg q24h[e]	IV
Staphylococcus spp.	Recommendation after completion of the initial IV treatment phase		
	Rifampin *plus*	450 mg q12h or 600 mg q24h[b]	PO
	Levofloxacin *or*	750 mg q24h to 500 mg q12h	PO
	Ciprofloxacin *or*	750 mg q12h	PO
	Teicoplanin *or*	400 mg q24h[f]	IV
	Fusidic acid *or*	500 mg q8h	PO
	Trimethoprim-sulfamethoxazole *or*	1 DS tablet q8h[g]	PO
	Minocycline[h] *or*	100 mg q12h	PO
	Linezolid *or*	600 mg q12h	PO
	Clindamycin[i]	1200–1350 mg/day divided in 3–4 doses	PO
Streptococcus spp.[j]	Penicillin G[c] *or*	18–24 million U/day divided in 6 doses	IV
	Ceftriaxone for 4 wk, *followed by*	2 g q24h	IV
	Amoxicillin *or*	1000 mg q8h	PO
	Clindamycin[i]	1200-1350 mg/day divided in 3–4 doses	PO
Enterococcus spp.[k]			
Ampicillin or amoxicillin susceptible			IV
	Ampicillin *or* amoxicillin[l] *or*	2 g q4h–q6h	IV
Ampicillin or amoxicillin resistant	Vancomycin *or*	15 mg/kg q12h[d]	IV
	Daptomycin *or*	6–10 mg/kg q24h[e]	IV
	Linezolid	600 mg q12h	IV/PO
Enterobacteriaceae	β-Lactam based on in vitro susceptibilities for 2 wk[m] *followed by*		IV
	Ciprofloxacin	750 mg q12h	PO
Enterobacter spp.[n]	Cefepime *or*	2 g q8h	IV
	Ceftazidime *or*	2 g q8h	IV
	Ertapenem *or*	1 g q24h	IV
	Meropenem	1 g q8h[o]	IV
	for 2–4 wk, *followed by*		
	Ciprofloxacin	750 mg q12h	PO
Nonfermenters[p] (e.g., *Pseudomonas aeruginosa*)	Cefepime *or*	2 g q8h	IV
	Ceftazidime *or*	2 g q8h	IV
	Meropenem	1 g q8h[p]	IV
	for 2–4 wk, *followed by*		
	Ciprofloxacin	750 mg q12h	PO
Cutibacterium spp.	Penicillin G *or*	18–24 million U/day divided in 6 doses	IV
	Clindamycin[i]	600–900 mg q8h	IV
	for 2-4 wk *followed by*		
	Amoxicillin *or*	1000 mg q8h	PO
	Clindamycin[i]	1200–1350 mg/day divided in 3–4 doses	PO
Gram-negative anaerobes (e.g., *Bacteroides* spp.)	Metronidazole	500 mg q8h	IV/PO