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Review article

Microbiology and management of joint and bone infections due to anaerobic bacteria

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Abstract
Purpose. To describes the microbiology, diagnosis, and management of septic arthritis and osteomyelitis due to anaerobic bacteria.
Results. The predominant anaerobes in arthritis are anaerobic Gram-negative bacilli (AGNB) including the *Bacteroides fragilis* group, *Fusobacterium* spp., *Peptostreptococcus* spp., and *Propionibacterium acnes.* Infection with *P. acnes* is associated with a prosthetic joint, previous surgery, and trauma. *B. fragilis* group is associated with distant infection, *Clostridium* spp. with trauma, and *Fusobacterium* spp. with oropharyngeal infection. Most cases of anaerobic arthritis, in contrast to anaerobic osteomyelitis, involved a single isolate, and most cases are secondary to hematogenous spread. The predominant anaerobes in osteomyelitis are *Bacteroides, Peptostreptococcus*, *Fusobacterium,* and *Clostridium* spp. as well as *P. acnes*. Conditions predisposing to bone infections are vascular disease, bites, contiguous infection, peripheral neuropathy, hematogenous spread, and trauma. Pigmented *Prevotella* and *Porphyromonas* spp. are mostly isolated in skull and bite infections, members of the *B. fragilis* group in hand and feet infections, and *Fusobacterium* spp. in skull, bite, and hematogenous long bone infections. Many patients with osteomyelitis due to anaerobic bacteria have evidence of an anaerobic infection elsewhere in the body that is the source of the organisms involved in the osteomyelitis. Treatment of arthritis and osteomyelitis involving anaerobic bacteria includes symptomatic therapy, immobilization in some cases, adequate drainage of purulent material, and antibiotic therapy effective against these organisms.
Conclusions. Anaerobic bacteria can cause septic arthritis and osteomyelitis. Correct diagnosis and appropriate therapy are important contributor to successful outcome.

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Introduction

Infections attributed to anaerobic bacteria are commonly unrecognized and may be serious and life-threatening. The increased recovery of these organisms has led to greater appreciation of the role anaerobes play at all body sites, including the joints and bones.

Anaerobes are the predominant components of normal human skin and mucous membrane bacterial flora[1] and therefore are a common cause of bacterial infections of endogenous origin. Because of their fastidious nature, these organisms are difficult to isolate from infectious sites and often are overlooked. Their exact frequency is difficult to ascertain because of the inconsistent use of methods for isolation and identification. The lack of adequate therapy against these organisms may lead to clinical failure. Their isolation requires appropriate methods of collection, transportation, and cultivation of specimens.[1] Treatment of anaerobic infection is complicated by the slow growth of these organisms, their polymicrobial nature, and the growing resistance of anaerobic bacteria to antimicrobial agents.

This review describes the microbiology and management of septic arthritis and osteomyelitis attributed to anaerobic bacteria.

Septic arthritis

Septic arthritis is defined as a purulent infection in a joint cavity. The infection commonly reaches the joint by hematogenous spread or by direct extension of pathogenic bacteria.

Microbiology

Staphylococcus aureus is a predominant etiological agent of septic arthritis in all age groups. A history of

trauma is often associated with *S. aureus* infection.[1,2] This organism causes more than three-fourths of infections in joints affected by rheumatoid arthritis. Neisseria gonorrhoeae is the most frequent pathogen among young, sexually active individuals. *Streptococcus* spp., such as Streptococcus viridans, Streptococcus pneumoniae, and groups A and B streptococci, account for 20% of cases. Aerobic Gram-negative rods cause about 20%–25% of cases. Most of these infections occur in the very young or old, the immunosuppressed, and intravenous drug abusers. In newborns, however, group B β-hemolytic streptococci and Gram-negative enteric organisms are also involved. *Haemophilus influenzae* type b, *S. aureus*, group A streptococci, and *Streptococcus pneumoniae* cause arthritis in children younger than 5 years of age. *H. influenzae* type b infection is, however, now rare in immunized children.[3,4] *S. aureus* and group A streptococci are the most common causes of arthritis in children older than 5 years.

Other organisms reported to cause pyogenic arthritis in children include *Kingela kingae*,[5] *Neisseria meningiditis*,[6] *Salmonella* spp.,[7] and anaerobic bacteria.[8,9] Gonococcal arthritis can occur in sexually active adolescents.

In intravenous drug addicts, enteric bacteria, *Pseudomonas aeruginosa*, and *Candida* spp. can cause septic arthritis, especially in the sternoclavicular joint and intervertebral disc space.[10]

Rare causes of septic arthritis include mycobacteria,[11] *Mycoplasma pneumoniae*, Borrelia burgdorferi, fungi[11,12] (e.g., *Candida albicans*, Histoplasma spp., Sporothrix schenckii, Coccidioides immitis, Blastomyces spp.),[12,13] and viruses (e.g., human immunodeficiency virus, lymphocytic choriomeningitis virus, hepatitis A, B, and C viruses, rubella virus).

The occurrence of prosthetic joint infections can be divided into three time periods: within 3 months of implantation; 3–24 months after implantation; and ≥24 months following the implantation. Most early prosthetic joint infections are caused by S. aureus, whereas delayed infections are caused by Staphylococcus epidermidis and Gram-negative aerobes.[14] Both of the earlier infections (i.e., at 0–24 months) are acquired during the surgical procedure, whereas the late infections (at ≥24 months) are secondary to hematogenous spread from various infectious foci.

Anaerobes rarely have been reported as a cause of septic arthritis in children. Feigin et al.[15] reported two children with septic arthritis caused by clostridia. Nelson and Koontz[16,17] reported 3 of 219 patients with septic arthritis: one with *Clostridium novyi*, one with *Clostridium bifermentans*, and one with *Bacteroides funduliformis*. Sanders and Stevenson,[18] reviewed the literature published before 1968 regarding *Bacteroides* infections in children and reported five patients, two of whom were their patients and three reported by others.[19,20] Sanders and Stevenson's patients also had agammaglobulinemia.

A review of all the adult and pediatric literature by Finegold[21] revealed 1236 joint infections involving anaerobic bacteria. Most of these cases were reported from the preantimicrobial era; and the most common anaerobe was *Fusobacterium necrophorum*, accounting for one-third of the recovered anaerobes.

Anaerobic Gram-negative bacilli (AGNB), including the *Bacteroides fragilis* group, and fusobacteria and Gram-positive anaerobic cocci were also recovered from patients with septic arthritis involving anaerobes.[22] Sternoclavicular joint infection due to *Prevotella oralis* was reported.[23] Hip arthritis due to *Fusobacterium necrophorum* was described after tonsillectomy in a 9-year-old boy.[24] *Propionibacterium acnes* is associated with arthritis in prosthetic joints[25] and after arthroscopy.[26] The joints most frequently involved with anaerobic infection were the larger ones, especially the hip and knee, and less frequently the elbow and shoulder.

Most of the cases of anaerobic arthritis, in contrast to anaerobic osteomyelitis, involved one isolate. Approximately 8% involved mixed bacterial flora.

Fitzgerald et al.[27] reported 43 patients ranging in age from 10 to 78 years with anaerobic septic arthritis. Postoperative infection after arthroplasty was present in 23 patients, posttraumatic infection in 12, and arthritis with underlying debilitating diseases in 8. Anaerobic Gram-positive cocci, especially *Peptostreptococcus magnus*, were the predominant anaerobic isolates in cases of postsurgical and posttraumatic septic arthritis. These organisms probably originate from the skin's normal flora, in contrast to the previously recognized association of *Clostridium* spp. with traumatic injuries. In contrast, patients with anaerobic arthritis with underlying debilitating disease were infected with AGNB, especially *Bacteroides fragilis*. Fitzerald et al.[27] were also able to recover similar organisms from the blood of seven of their patients. These patients had concomitant distant infections such as intraabdominal sepsis, decubitus ulcers, and osteomyelitis.

Brook and Frazier studied 65 infected joints for aerobic and anaerobic bacteria in adults.[28] A total of 74 organisms (1.1 isolates/specimen), consisting of 67 anaerobic bacteria and 7 facultative or aerobic bacteria, were isolated from the 65 joint specimens. The predominant anaerobes were *P. acnes* (24 isolates), anaerobic cocci (17), AGNB (10), and *Clostridium* spp. (5). Infection with *P. acnes* was associated with a prosthetic joint, previous surgery, and trauma. *B. fragilis* group was associated with distant infection, *Clostridium* spp. with trauma, and *Fusobacterium* spp. with oropharyngeal infection.

Pathogenesis

During the initial stages, there is an effusion in the joint cavity that rapidly becomes purulent. Destruction of cartilage occurs at areas of joint contact. Bone is not affected during the early stages; but the femoral and humeral heads, if involved, may undergo necrosis and subsequent fragmentation and pathological dislocation. Epiphyses with synchondroses located within the joint capsule are at particularly high risk for infection and necrosis.

During the chronic and repair phases of the disease the exudate is organized, and granulation tissue appears and becomes fibrous. This may bind the joint surfaces together, causing fibrous ankylosis. When motion is present, the synovial fluid tends to regenerate, but limitation of motion and associated pain generally remain as a result of residual strong intrasynovial adhesions having been produced.

Most cases of anaerobic arthritis are secondary to hematogenous spread. Almost all of the isolates of AGNB, including the fusobacteria and the Gram-positive anaerobic cocci that were reported, were also involved in a concomitant anaerobic sepsis. In contrast, arthritis secondary to a penetrating wound or foreign body is associated with clostridia.[20,27]

Conditions that predispose to joint infection are trauma, prior surgery, presence of a prosthetic joint, and contiguous infection.[28] *P. acnes* isolates were associated with prosthetic joints, members of the *B. fragilis* group with hematogenous spread, and *Clostridium* spp. with trauma.

The presence of multiple septic joints was common in cases in which there was spread of the organisms from a primary site through the bloodstream or in cases of endocarditis.[20] The ability of anaerobes to cause tissue destruction is reflected in the amount of damage they can inflict on the joints, cartilage, capsule, and adjacent periosteum.

Diagnosis

Systemic findings such as fever, malaise, and vomiting may be present. Pain may be severe; motion is limited, and the joint is splinted by muscular spasm. In infants, this may produce pseudoparalysis. An effusion occurs but may not be palpable at first. The overlying tissues become swollen, tender, and warm. As the infection proceeds, contractures and muscular atrophy may result. Polyarticular arthritis is generally seen with gonococcal disease, viral infections, Lyme disease, reactive arthritis, and various noninfectious processes. Reactive arthritis usually involves a few large joints in an asymmetrical fashion. Viral arthritis often exhibits symmetrical involvement of the smaller joints, mostly the hands, with a concurrent rash.

Radiographic examination may reveal joint capsule distention and subsequent narrowing of the cartilage space, erosion of the subchondral bone, irregularity and fuzziness of the bone surfaces, bone destruction, diffuse osteoporosis, and associated osteomyelitis. Radiological examination of the joint also may be useful for detecting unsuspected fracture or chronic bone or joint disease. Plain radiographs can be normal in children with proven pyogenic hip arthritis.[29]

Radionuclide scans (i.e., technetium 99m, gallium 67, indium 111 leukocyte scans) are used to localize areas of inflammation nonspecifically and can be valuable for evaluating involvement of the hip or sacroiliac joints. Computed tomography (CT) can be helpful in the diagnosis of arthritis of the shoulder, hip, and sacroiliac joint.

Magnetic resonance imaging (MRI) is highly sensitive for early detection of joint fluid.[30] Positive findings include high-signal periarticular changes and periarticular abscesses in some cases. MRI can delineate abnormalities of soft tissue, adjacent bone, and the extent of cartilage destruction. Other helpful tests include the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, which generally are elevated[31]; peripheral leukocyte count, which is generally increased; and blood cultures, which may reveal the causative organisms.

Arthrocentesis can provide a rapid diagnosis of suppurative arthritis. The joint fluid should be examined for glucose (which is generally reduced compared to serum levels)[32] and the leukocyte count (which is generally elevated above 50 000 cells/mm^3).[33] A Gram stain should be done and cultures prepared to detect aerobic, anaerobic, fungal, and mycobacterial organisms. At least two blood cultures should be performed. The polymerase chain reaction (PCR) can assist in detecting infective arthritis due to *Yersinia* spp., *B. burgdorferi*, *Chlamydia* spp., *N gonorrhoeae*, and *Ureaplasma* spp.

The joint fluid may have a foul odor in the case of anaerobic infection, and rarely there is gas under pressure in the joint. Other clues to purulent arthritis involving anaerobes include failure to obtain organisms on routine culture, Gram stain of the joint fluid showing organisms with the unique morphological characteristics of anaerobes, and evidence of anaerobic infection elsewhere in the body.

An early and accurate diagnosis of septic arthritis is clinically important. Differentiating infectious arthritis from noninfectious inflammatory synovitis is a frequent diagnostic problem. Synovial fluid analysis often does not yield a diagnosis despite careful bacteriological examination, especially in partially treated cases.[32]

Brook et al.[34] studied the joint fluid of 84 patients with acute arthritis. Their data suggest that lactic acid

Table 1. Antimicrobial drugs of choice for anaerobic bacteria

Bacterium	First	Alternate
Peptostreptococcus spp.	Penicillin	Clindamycin, chloramphenicol, cephalosporins
Clostridium spp.	Penicillin	Metronidazole, chloramphenicol, cefoxitin, clindamycin
C. difficile	Vancomycin	Metronidazole, bacitracin
Fusobacterium spp.	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL−)	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL+)	Metronidazole, a carbapenem, a penicillin, and BL inhibitor clindamycin	Cefoxitin, chloramphenicol, piperacillin, tigecycline

BL, β-lactamase

measurements of joint fluid may clearly differentiate between septic arthritis (other than gonococcal arthritis) and other sterile inflammatory and noninflammatory conditions in the joints. Lactic acid levels <65 mg/dl should be considered highly suggestive of the presence of a bacterial infection. The synovial fluid also can be studied for bacterial antigens by immunoelectrophoresis or gas-liquid chromatography.[35,36]

Treatment

Parenteral antibiotic therapy should be initiated immediately after aspirating the joint. The choice of therapy should be directed by results of the Gram stain and bacterial cultures. Adequate penetration into the joint is essential.

Therapy of anaerobic arthritis is not different from that required for arthritis caused by aerobes. It includes treating any underlying disease, appropriate drainage and débridement, temporary immobilization of the joint, and antimicrobial therapy pertinent to the bacteriological characteristics in the individual patient.

Ceftriaxone or fluoroquinolones are effective against *N. gonorrhoeae*. β-Lactamase-resistant penicillins (e.g., oxacillin) or first-generation cephalosporins are effective against *S. aureus* infection. However, because of the recent increase in the isolation of methicillin-resistant *S. aureus* (MRSA), patients with serious staphylococcal infections should be initially given an agent active against MRSA until susceptibility results are available. Vancomycin, daptomycin, linezolid, and quinupristin/dalfopristin can be administered to treat these infections. A combination of a penicillin and a β-lactamase inhibitor (e.g., amoxicillin or ticarcillin plus clavulanic acid) or a third-generation cephalosporin is administered for *H. influenzae* until the antimicrobial susceptibility report is available. Clindamycin, cefoxitin, a carbapenem (e.g., imipenem, meropenem, ertapenem), tigecycline, or the combination of a penicillin and a β-lactamase inhibitor are alternative drugs, as they affect *S. aureus* and most anaerobic bacteria. Another agent that is effective only against anaerobic bacteria is metronidazole. When specific anaerobic organisms are isolated, empirical coverage against them can be chosen according to their predicted antimicrobial susceptibility (Tables 1, 2) and later their specific susceptibility. Empirical coverage against an infection due to mixed aerobic-anaerobic organisms can be made according to their predicted antimicrobial susceptibility (Table 3) and later their specific susceptibility.

The exact duration of antimicrobial therapy has not been determined; however, it should be given for at least 3–4 weeks in mild cases. Orally administered antibiotics can be substituted for parenteral treatment after adequate control of infection and inflammation if compliance and monitoring are possible.[37]

Surgical drainage of the joint may be required when fluid rapidly reaccumulates after the initial diagnostic drainage is done, when the appropriate antibiotic and vigorous percutaneous drainage fail to clear the infection after 5–7 days, if the infected joints are difficult to aspirate (e.g., hip), or if the adjacent soft tissue is infected. Pus may be drained by intermittent aspiration or by open incision and drainage followed by continuous suction irrigation. Débridement is performed by arthroscopy in some cases of pyogenic arthritis of the knee.[38]

Osteomyelitis

Osteomyelitis is an acute or chronic pyogenic inflammatory process that may involve all parts of a bone, although the initial focus usually involves the metaphysis.

Microbiology

The etiology of acute hematogenous osteomyelitis varies with age. In newborns, *S. aureus*, *Enterobacter* spp., and group A and B streptococci predominate. *S. aureus*, group A streptococci, *H. influenzae*, and *Enterobacter* spp. are most often found in children 4 months

Table 2. Antimicrobial agents effective for treating anaerobic infections

Antimicrobial	Route of administration	Dose and interval		
		Newborns (mg/kg/day)	Children <40 kg (mg/kg/day)	Adults and children >40 kg
Penicillin G	IV, IM	50 000–100 000 units (q8–12h)	100 000–250 000 units (q4h)	10–20 million units/day
Ticarcillin + clavulanic acid	IV	150–225 (q8–12h)	200–300 (q4–6h)	3.1 g (q4–8h) to 6.2 g (q6h)
Amoxicillin + clavulanic acid	POl	N/A	20–40 (q8h)	250–500 mg (q8h)
Ampicillin + sulbactam	IV	N/A	50–100 (q6h)	1.5–3.0 g (q6h)
Piperacillin + tazobactam	IV	N/A	75 (q12h)	3.375 g (q6h)
Cefoxitin	IM, IV	N/A	80–160 (q4–6h)	1–2 g (q4–6h)
Chloramphenicol	IV or PO	25 mg once a day	50–75 (q6h)	1 g (q6h)
Clindamycin	IM, IV	10–15 (q8–12h)	25–40 (q6–8h)	600 mg (q6h), 900 mg (q8h)
	PO	10–15 (q8–12h)	10–30 (q6h)	150–450 mg (q6h)
Metronidazole	IV	15 (q12h)	30 (q6h)	500–1000 mg
	PO	15 (q12h)	15–35 (q8h)	500 mg (q6h)
Imipenem	IV	N/A	40–60 (q6h)	250–500 mg (q4–6h)
Meropenem	IV	N/A	60–120 (q8h)	500–1000 mg (q8h)
Ertapenem	IM, IV	N/A	15 (q12h)	1.0 g q24h
Moxifloxacin	IV or PO	N/A	N/A[a]	400 mg q24h
Tigecycline	IV	N/A	1.5 initially, then 1q12h[a]	100 mg initially, then 50 mg q12h

N/A, not available
[a] Not approved for those under the age of 18 years

Table 3. Antimicrobial agents effective against mixed infection

Antimicrobial agent	Anaerobic bacteria		Aerobic bacteria	
	β-Lactamase-producing *Bacteroides*	Other anaerobes	Gram-positive cocci	Enterobacteriaceae
Penicillin[a]	0	+ + +	+	0
Chloramphenicol[a]	+ + +	+ + +	+	+
Cephalothin	0	+	+ +	+/–
Cefoxitin	+ +	+ + +	+ +	+ +
Imipenem/meropenem/ertapenem	+ + +	+ + +	+ + +	+ + +
Clindamycin[a]	++	+ + +	+ + +	0
Amoxicillin + clavulanic acid[a]	+ + +	+ + +	+ +	+ +
Piperacillin + tazobactam	+ + +	+ + +	+ +	+ +
Metronidazole[a]	+ + +	+ + +	0	0
Moxifloxacin[a]	++	++	++	+++
Tigecycline	++	+++	+++	++

Results are expressed in degrees of activity: 0 to + + +
[a] Available also in oral form

to 4 years of age, whereas in older children and adolescents *S. aureus*, group A streptococci, *H. influenzae*, and *Enterobacter* spp. are the most frequent isolates. In adults, the commonest species are *S. aureus* and occasionally *Enterobacter* or streptococci.

Staphylococcus aureus is the most common organism recovered from infected bones, accounting for more than half of the cases. Other causative agents are β-hemolytic streptococci and *S. pneumoniae*. *K. kingae*, *Bartonella henselae*, and *Borrelia burgdorferi*. Factors that predispose to the development of osteomyelitis include impetigo, furunculosis, burns, and direct trauma. Rare causes of osteomyelitis are mycobacteria, actinomycosis, and fungi.[39–44]

Osteomyelitis caused by direct extension is generally due to *S. aureus*, *Enterobacter* spp., and *Pseudomonas* spp. Wounds that occur through sneakers may be associated with *Pseudomonas* and *S. aureus* infections, and sickle cell disease is associated with *S. aureus* and *Salmonella* spp.

Brook and Frazier studied 73 specimens from infected bone.[28] Altogether, 157 organisms (2.2 isolates/specimen), consisting of 122 anaerobic bacteria (1.7 isolates/specimen) and 35 facultative or aerobic bacteria (0.5 isolate/specimen), were recovered from these specimens. Anaerobes were recovered along with aerobes or facultative bacteria in 24 (33%) instances. The predominant anaerobes were *Bacteroides* spp. (49 isolates), anaerobic cocci (45), *Fusobacterium* spp. (11), *P. acnes* (7), and *Clostridium* spp. (6). Conditions predisposing to bone infection are vascular disease, bites, contiguous infection, peripheral neuropathy, hematogenous spread, and trauma. Pigmented *Prevotella* and *Porphyromonas* spp. were mostly isolated in skull and bite infections, members of the *B. fragilis* group in hand and feet infection, and *Fusobacterium* spp. in skull, bite, and hematogenous long-bone infections.

Anaerobic bacteria have received increasing recognition in the bacteriology of osteomyelitis,[28,45,46] although the exact prevalence of anaerobes in this disease is unknown. More than 800 cases of bone infection involving anaerobic bacteria have been reported.[21] Many of these cases occurred in children; however, specific details are not given for this age group in most of these studies.

A few reports have described the recovery of anaerobic organisms from infected bones in children. Raff and Melo[46] reported the recovery of *S. aureus* mixed with *Eubacterium lentum* from osteomyelitis of the right femur of a 13-year-old patient. Schubiner et al.[47] recovered fusobacteria from an infected tibia in a 7-year-old patient with Gaucher's disease. Chandler and Breaks[48] reported recovery of *Bacteroides* spp. from the hip of a 12-year-old patient with osteomyelitis. Pichichero and Friesen[49] described a 9-year-old girl with paronychia and osteomyelitis of the phalanx. Six organisms were recovered from the infected site, including two anaerobes, *Prevotella melaninogenica* and *Veillonella parvula*. Sanders and Stevenson[18] reported a 3-year-old patient with Bruton's agammaglobulinemia and septic arthritis of the hip who had osteomyelitis of the femur caused by *Bacteroides* spp. Beigelman and Rantz[50] recovered *Bacteroides* spp. from an infected osteoma of the mandible in a 5-year-old patient. Ogden and Light[51] reported nine cases of anaerobic osteomyelitis in patients 3 months to 13 years of age. Four patients were malnourished, and three had sickle cell anemia. Seven patients had infections in the long bones, one had infection in the vertebrae, and one had infection in a metacarpal bone. *Bacteroides* spp. were recovered from six patients, *Clostridium* spp. from two patients, and anaerobic cocci from two patients. Garcia-Tornel et al.[52] described a 4-year-old girl with osteoarthritis of the right femur caused by *Bacteroides coagulans*. Many anaerobes have been recovered from children with infected mastoid bones.[53] Chronic osteomyelitis caused by *Clostridium difficile* was diagnosed in an adolescent with sickle cell disease.[54]

Ten years of experience in diagnosis and therapy of osteomyelitis caused by anaerobic bacteria in children was described by Brook,[55] who presented 26 pediatric patients with osteomyelitis caused by anaerobic bacteria. The etiological factors for the infections were chronic mastoiditis (7 patients), decubitus ulcers (5), chronic sinusitis (4), periodontal abscesses (3), bites (3), paronychia (2), trauma (1), and scalp infection after fetal monitoring (1). A total of 74 organisms (2.8 isolates/specimen) — 63 anaerobes (2.4/specimen) and 11 facultative and aerobic bacteria (0.4/specimen) — were recovered. The anaerobic bacteria that were recovered from all patients were mixed with aerobes in 11 (42%) patients. The predominant organisms were anaerobic cocci (29 isolates), AGNB (21), *Fusobacterium* spp. (8), and *Clostridium* spp. (4). The organisms generally reflected the microbial flora of the mucous membrane surface adjacent to the infected site. Eight β-lactamase-producing organisms were recovered from seven (27%) patients, including all isolates of the *B. fragilis* group (4) and of *S. aureus* (3), 2 of the 12 pigmented *Prevotella* and *Porphyromonas* spp., and 1 of 3 *Prevotella oralis*.

Finegold[21] reviewed the world literature on anaerobic osteomyelitis. He found that most of the cultures that yielded anaerobes also yielded aerobic or facultative organisms, except infections involving actinomycetes. When anaerobes are present in combination with aerobic organisms, they may act synergistically in producing disease. More than one-third of the isolates were AGNB, mainly *Bacteroides* and *Fusobacterium* spp. Other frequently recovered anaerobes were anaerobic Gram-positive cocci, actinomycetes, and *F. necrophorum*. Infections of long bones involved mainly clostridia; and vertebral osteomyelitis involved actinomycetes. Anaerobic Gram-positive cocci were recovered mostly from small bones of the extremities.

Two reports summarized more than 300 cases of nonactinomycotic anaerobic osteomyelitis, mostly in adults.[45,46] Lewis et al.[45] reviewed 260 patients and found an adjacent soft tissue infection in 49% of the patients. Fractures associated with trauma were a predisposing factor in 28% of the patients, approximately half in the long bones, and one-fourth each in the hands or feet and mandible or maxillae. Raff and Melo[46] reviewed 121 patients and also found fractures to be the most common etiological factor (occurring in 48%), followed by diabetes mellitus (11%), human bites (9%), otitis media (6%), and decubitus ulcers (4%).

These two reports[45,46] found infection in the skull and facial bones in approximately one-third of the cases, generally after chronic otitis media or sinusitis, facial cellulitis, dental abscesses or extractions, fractures, and

surgical procedures. Complications of these infections included meningitis, brain abscesses, and septic pulmonary infarctions.

The most common organisms responsible for these infections, as reported by Lewis et al.[45] and Raff and Melo,[46] were anaerobic Gram-positive cocci, *Bacteroides* spp., and *Fusobacterium* spp., all residents of the oral flora. Similar organisms were found to be the major pathogen in osteomyelitis of the skull and facial bones in children. However, in contrast to adults, osteomyelitis of the skull and facial bones accounted for 15 (57%) of the infections. The higher frequency of this type of infection in children may be related to the common occurrence of chronic otitis and sinusitis in the pediatric age group, compared with adults.

The polymicrobial nature of anaerobic osteomyelitis is apparent based on the data from these studies.[45,48,55] Mixed aerobic and anaerobic flora was recovered in 11 (42%) patients in the study by Brook,[55] and Lewis et al.[45] recovered 2.2 aerobes/specimen and 4.0 anaerobes/specimen from the 23 patients they studied.

Pathogenesis

Many patients with osteomyelitis caused by anaerobes have an anaerobic infection elsewhere in the body that is the source of the organisms involved in osteomyelitis. Spread to bone can be by a contiguous route or through the bloodstream during the course of sustained or intermittent bacteremia. This infection often shows characteristic features of an anaerobic infection, such as abscess formation, septic thrombophlebitis, production of a foul odor and gas, and tissue necrosis.[55] Some patients with anaerobic osteomyelitis also have arthritis involving anaerobes, generally in an adjacent joint.

A certain number of patients have positive blood cultures. Blood cultures were performed in 21 of the 26 patients reported by Brook and were positive in 4 (19%). The microorganisms recovered in these cultures were similar to those isolated from the infected site.

Diabetes mellitus and vascular insufficiency have been incriminated as predisposing factors in anaerobic infections.[56] Ischemia and necrotic tissue provide an optimum environment for invasion and proliferation of anaerobes.

Human bites frequently result in anaerobic osteomyelitis. Of patients with anaerobic osteomyelitis of the hand for whom a predisposing factor was given, more than two-thirds had sustained a human bite.[46,55]

The bacteria recovered from patients with osteomyelitis and decubitus ulcers generally reflect the normal bacterial flora of the closest mucous membrane and are also recovered from the infected ulcers.[57] Infections of the skull related to decubitus ulcers in that area were associated with anaerobes generally found in the oral flora, and infections that occurred after decubitus ulcers around the anal area were caused by colonic flora. Similarly, osteomyelitis of the occipital bone after fetal monitoring has been caused by organisms that are normal residents of the female genital tract and were thus believed to have been introduced by the monitoring electrodes.

Many other conditions may predispose to invasion of bone by anaerobic bacteria. Among them are chronic otitis media, decubitus ulcers, abscesses, chronic sinusitis, and odontogenic infections.[58] Several reports of anaerobic osteomyelitis have also shown direct extension of anaerobic infection from adjacent sinusitis[57,59] or direct implantation of the organisms from oral[59,60] or vaginal[61] flora.

Diagnosis

Local inflammatory signs may be absent during the early stages. Later, there is usually localized erythema, warmth, tenderness, and swelling; fever; an elevated pulse; pain that is severe, constant, and throbbing over the end of the shaft; and limitation of joint motion. Laboratory findings may reveal leukocytosis, an elevated ESR, and increased CRP level.[62–64] Blood cultures are generally positive early in the course. Examining smears of aspirated pus and performing aerobic and anaerobic cultures of the pus are essential.

At 3–5 days after infection, radiographs may show soft tissue edema. A spotty rarefaction may be observed, followed shortly by periosteal new bone formation, generally absent for the first 10–14 days of the disease.[65–67] A considerable portion of bone usually is involved, and the bone is demineralized. Radionuclide scanning with a three-phase technetium 99m bone scan may be positive before bony changes are seen on the radiograph.[65–67] MRI can be an effective means of imaging bone,[68,69] with the sensitivity for early detection of osteomyelitis ranging from 92% to 100%. It is superior to plain radiography, CT, and radionuclide scanning in selected anatomical locations.[70] MRI can differentiate cellulitis from osteomyelitis as well as acute from chronic osteomyelitis.[71] Ultrasonography may demonstrate changes as early within 24–48 hours after the onset of symptoms. It can detect a soft tissue abscess or fluid collection and periosteal elevation, and it can be used to guide an aspiration procedure.

There are no significant clinical differences between the patients with and without anaerobes cultured from their bone infections. There is a relative lack of systemic symptoms in patients with bone infections involving anaerobes.[39] Foul odor is present in approximately half of the patients.[46,55]

The importance of obtaining adequate specimens for Gram stain and culture cannot be overemphasized.

Many cases of culture-negative osteomyelitis may have been caused by anaerobes that were not detected. Aliquots of bone obtained either by needle biopsy or as surgical specimens should be placed in media immediately under conditions appropriate for isolating obligate anaerobic pathogens.

Although the clinical presentation of anaerobic or mixed aerobic and anaerobic osteomyelitis may not differ markedly from that of aerobic osteomyelitis, anaerobic osteomyelitis should be suspected in particular clinical settings.

1. Hand infections occurring as a result of bites
2. Osteomyelitis of the pelvis or ilium after intraabdominal sepsis
3. Osteomyelitis following decubitus ulcers
4. Patients with osteomyelitis of the skull and facial bones
5. Chronic nonhealing indolent ulcers of the foot, particularly in diabetics or in patients with associated vascular insufficiency who have underlying foci of bony involvement
6. Presence of foul-smelling exudates
7. Presence of sloughing of necrotic tissue, gas in soft tissues, and/or black discharge from a wound
8. Gram stains of clinical material that reveals multiple organisms having different morphological characteristics
9. Failure to grow organisms from clinical specimens, particularly but not only when the Gram stain has shown organisms
10. Presence of sequestra in the bone
11. Presence of exacerbation of chronic osteomyelitis of long bones

Treatment

Management of osteomyelitis includes symptomatic therapy, immobilization for some patients, adequate drainage of purulent material, and antibiotic therapy consisting of parenteral administration of antibiotics for at least 4–8 weeks and in some cases even longer. The average duration of antimicrobial therapy for patients in the previous reported study was 31 days (range 22–58 days). Other than for diagnostic aspiration, extensive surgical drainage or débridement was performed in 18 (60%) of our patients.[55] This included all patients with mastoiditis, sinusitis, periodontal abscess, fetal monitoring, two of five with decubitus ulcer, and one of two with paronychia.

Although antibiotic therapy most often is started before culture results are available, treatment programs must be adjusted for the sensitivities of microorganisms recovered from bone cultures obtained by needle aspiration or surgery or from blood cultures. Once specimens for culture are obtained, it is important to initiate therapy without delay if treatment failures and structural complications are to be avoided.

Numerous factors must be considered when antibiotics are selected. The least toxic agent should be given at doses that yield the optimal inhibitory concentration for a period long enough to inhibit all dormant organism(s). Culture information is essential to this choice. In general, the penicillins, cephalosporins, clindamycin, and vancomycin have achieved clinically effective bone concentrations against staphylococci. Clindamycin has especially good bone penetration, attaining a high bone-to-serum ratio.[71]

For the most common isolate, *S. aureus*, the preferred drug is a β-lactamase-resistant penicillin. Alternatives are the cephalosporins, clindamycin, and vancomycin. Antimicrobials effective against MRSA include vancomycin, daptomycin, tygecycline, linezolid, and quinupristin/dalfopristin. Other Gram-positive organisms, such as group A and B streptococci, *S. pneumoniae*, clostridia, actinomycetes, and Gram-positive anaerobic cocci usually are penicillin-sensitive. Aerobic and facultative gram-negative microorganisms should be treated with third-generation cephalosporins, quinolones (after closure of the epiphyseal line), and aminoglycosides.

Penicillin G is the preferred drug for most anaerobic infections other than those caused by *B. fragilis* group.[21,72] The *B. fragilis* group is known to resist penicillin through production of β-lactamase. Many AGNB (e.g., pigmented *Prevotella* and *Porphyromonas* spp.) and *Fusobacterium* spp., which formerly were susceptible to penicillins, have shown increased resistance to these drugs, achieved by producing β-lactamase.[73] This phenomenon was also observed in our report[55] in which five of the AGNB produced β-lactamase. When such organisms are present, an antimicrobial that is resistant to this enzyme should be used. Such agents include clindamycin, chloramphenicol, cefoxitin, tygecycline, a carbapenem (i.e., imipenem, meropenem), metronidazole, or the combination of a β-lactamase inhibitor and a penicillin.[74]

When specific anaerobic organisms are isolated, empirical coverage against them can be chosen according to their predicted antimicrobial susceptibility (Tables 1, 2) and later their specific susceptibility. Empirical coverage against an infection due to mixed aerobic-anaerobic organisms can be accomplished based on their predicted antimicrobial susceptibility (Table 3) and later their specific susceptibility.

Surgical intervention often is required to establish a diagnosis and to remove foreign material. Otherwise, surgery is limited therapeutically to patients in whom drainage of a subperiosteal collection or débridement of necrotic or devitalized bone is necessary. Failure to respond to appropriate treatment coupled with contin-

ued pain, swelling, fever, and elevated leukocyte count and ESR are indications for surgery. For vertebral osteomyelitis complicated by neurological compromise, immediate surgical intervention is required to relieve cord compression. Surgery also should be used to drain a septic hip when it accompanies osteomyelitis.

The usual duration of therapy is 4–8 weeks, depending on the etiology, extent of infection, and clinical and laboratory responses. A change to oral antibiotics can be made when pain, fever, and signs of local inflammation have resolved, although it depends on the willingness of the patients to comply with an oral medication regimen and the likelihood of their adherence to it.

Hyperbaric oxygen also may be considered as adjunctive therapy for anaerobic osteomyelitis.[75] Slack et al.[76] treated five patients with chronic osteomyelitis caused by aerobic organisms and had encouraging results. Others[77–79] have reported various degrees of success in the treatment of patients with wound infections caused by aerobic organisms and in experimental treatment of staphylococcal osteomyelitis.[80]

Although anaerobic osteomyelitis occurs infrequently, if it is unrecognized or inappropriately treated the infection can lead to severe local and systemic complications. Early recognition, use of appropriate diagnostic and laboratory methods, and proper medical and surgical treatment can contribute to rapid resolution of the infection.

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