Osteomyelitis: a current challenge

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ABSTRACT

Over the last 30 years, the pathogenesis of osteomyelitis has almost been totally elucidated, and many factors responsible for the persistence of this infection have been identified. Numerous antimicrobial agents with distinct spectrums of action, pharmacokinetics, and pharmacodynamics have been used in its treatment. Surgical techniques, including muscle grafts, the Ilizarov technique, and antibiotic bone cements, have been applied. However, bone infections are still a challenge. Despite the importance of isolation and identification of microorganisms to determine the antimicrobial treatment of bone infections, there are few systematic national studies about the etiological profile of these diseases. This article describes the current knowledge of osteomyelitis and summarizes published national data based on the experience of different Orthopedic and Traumatology Services. In general, *S. aureus* was described as an important etiological agent; however, the difference in design of national studies makes a comparison between the prevalence of bone infection, the associated risk factors, and the different therapeutic approaches difficult. In conclusion, effort is necessary in order to stimulate systematic national studies in different Orthopedics and Traumatology Services to obtain a better consensus on preventive measures and therapies of bone infections.

Keywords: osteomyelitis, arthroplasty, *S. aureus*.

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INTRODUCTION

Osteomyelitis is a progressive infection that results in inflammatory destruction, necrosis, and bone neoformation, which can progress to a chronic and persistent stage.[1] However, it is not a single entity; this disease is differentiated according to the etiology, pathogenesis, and degree of bone involvement, as well as age and the immune condition of the patient.[2] It can involve different structures such as the bone marrow, cortex, periosteum, and parts of the surrounding soft tissues, or remain localized. Given this heterogeneity, several methods of classification have been proposed. However, the models of Waldvogel *et al.*[3] and of Cierny-Mader[4] are the most accepted.[5] Waldvogel's system is based on duration, mechanism of infection, and presence of vascular insufficiency, providing the following classification: a) acute hematogenic osteomyelitis; b) osteomyelitis by contiguity, with or without vascular inadequacy; c) vertebral osteomyelitis; and d) chronic osteomyelitis.[3] On the other hand, the Cierny-Mader's classification is focused on the portion of the affected bone and the physiological state of the host, including local (chronic lymphedema, venous stasis, retained foreign bodies, etc.) and systemic risk factors (tobacco abuse, immune deficiencies, malnutrition, etc.).[3-7] According to Sia & Berbari.[5] the latter classification has more evident clinical significance in treatment and prognosis of osteomyelitis, since it is more comprehensive, including considerations of other risk factors besides patient's bone injury. Regardless of the model adopted, the distinct types of osteomyelitis require different clinical and surgical therapeutic strategies. The most common bone infections in decreasing order are: osteomyelitis secondary to a contiguous-focus of infection or by direct inoculation (contamination after trauma or due to surgery); osteomyelitis due to vascular insufficiency and infection of surrounding soft tissues with the bone initially unaffected, including diabetic foot, and, finally, infections originating from the bloodstream in which the origin of the infection is distant.[5,8] Bloodstream-sourced infections generally involve the metaphysis of long bones in children or

vertebral bodies in adults.[2,9,10] While the incidence of acute hematogenous osteomyelitis has been reducing in under 13-year-old children,[11,12] bone infections by direct inoculation have increased over the last decades. This is probably due to high-energy accidents and the growing use of orthopedic fixation devices and joint prostheses.[13] When genders are compared, men present with a higher rate of contiguous-focus osteomyelitis.[14] In fact, men are more frequently involved in automobile accidents, which tend to cause exposed fractures with consequent high rates of infection.[15]

Microbial etiology of osteomyelitis

Bone tissue is relatively resistant to infection. However, osteomyelitis may occur after a great inoculation of microorganisms or even by a small inoculation of particularly virulent bacteria. Thus, the occurrence, type, severity, and the prognosis of osteomyelitis depends on the inter-relationship of a triad composed of characteristics inherent to the infection, the host, and the infecting pathogen.[12]

Table 1 shows osteomyelitis according to the type, age/susceptibility factors of the host, and microbial etiology. Hematogenous osteomyelitis is generally monomicrobial,

Table 1. Osteomyelitis according to type, age/susceptibility factors of the host and microbial etiology (in bold, the most frequent situation and isolated microorganisms)

Types of osteomyelitis	Age/Susceptibility factors	Etiology
Bloodstream-sourced		
	Adults	*Staphylococcus aureus*
	Newborn babies	*Enterobacteriaceae, Streptococcus agalactiae*
	Children	***S. aureus,*** *Streptococcus pyogenes,* Group B *streptococci, Haemophilus influenzae*
	Sickle cell disease	*Salmonella* spp., *S. aureus*
	Intravenous drug abuse	*S. aureus, Pseudomonas. aeruginosa, Candida* spp.
Vertebral		
	Adults	***S. aureus***
	Urinary infection	Aerobic gram-negative bacilli, *Enterococcus* spp.
	Injectable drug users	*P. aeruginosa, S. aureus, Serratia marcescens*
	Spinal column surgery	Coagulase-negative *staphylococci, S. aureus,* aerobic gram-negative bacilli
	Infection of vascular devices	*Candida* spp.
	Endemicity	*M. tuberculosis, Brucella* spp.
Contiguous-focus		
	Diabetes mellitus, vascular insufficiency, contaminated exposed fracture	**Polymicrobial:** *S. aureus,* coagulase-negative *staphylococci, Streptococcus* spp., *Enterococcus* spp., gram-negative bacilli, anaerobic
	Contamination of the soil	*Clostridium* spp., *Bacillus* spp., *Stenotrophomonas maltophilia*, *Nocardia* spp., atypical mycobacteria, *Aspergillus* spp., *Rhizopus* spp., *Mucor* spp.
	Orthopedic fixation devices	*S. aureus*, coagulase-negative *staphylococcus, Propionibacterium* spp.
	Human or animal bites	*Pasteurella multocida, Eikenella corrodens*
	Foot lesion by sharp object or nail	*P. aeruginosa*
	Previous periodontal infection	*Actinomyces* spp.
	Hospitalization (nosocomial source)	*Enterobacteriaceae, P. aeruginosa, Candida* spp.
Chronic		
	Fractures	***S. aureus***
	Ischemic ulcers (diabetes mellitus; sickle cell disease; malnutrition)	**Gram-negative bacilli, anerobe bacteria**

Adapted from Mackowiak *et al.*, 1978,[44] and Lew & Waldvogel, 2004.[8]

that is, a single bacterial species is isolated at the infection site.[3,16,17] Among newborn babies, the most common bacteria found in bone infections are *Streptococcus agalactiae* and *Escherichia coli*, while *S. aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* predominate in children. The incidence of osteomyelitis by H. *influenzae* has reduced after the introduction of routine active immunization during childhood.[12] *S. aureus* is the most common microorganism isolated in adults, while other pathogens are less frequently found including *Enterococcus* spp., *Streptococcus* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp., *Mycobacterium* spp., anaerobes, and fungi, specifically *Candida* spp.[10]

In vertebral osteomyelitis, although *S. aureus* is the predominant agent, gram-negative bacilli are frequently detected and may originate from the urinary tract and via injected drugs. In this setting, the incidences of *P. aeruginosa* and *Serratia marcescens* are high.[18,19] In contiguous-focus osteomyelitis, with a notable polymicrobial etiology, *S. aureus* and coagulase-negative staphylococci are most commonly isolated, corresponding to 75% of the etiological agents,[3,16,17] as well as gram-negative bacilli and anaerobic organisms. High rate of nasal and skin colonization by *S. aureus*, immunity disorders, and irregular scaring of pre-existent wounds are important in infections involving diabetic foot. This is understandable, since the skin lesions caused by superficial fungal infections, most common in these patients, represent a bacterial entry.[20]

S. aureus is the typical pathogen responsible for both acute and chronic osteomyelitis by forming a biofilm, with potential to rapidly develop antimicrobial resistance and expression of virulence factors, regardless of patient's immune status. In these cases, surgical intervention is necessary to control the infection. This bacterium is a member of the normal flora of the human nasal cavity with, approximately, 20% of people within a population colonized by these microorganisms in a persistent manner, while another 60% are transiently colonized.[21] Due to its high virulence, *S. aureus* may cause several diseases, from localized superficial infections, such as skin infections, to the most severe forms of bacteremia, such as septic arthritis, endocarditis, and septic shock syndrome. This situation becomes more complex with the emergence of multiple drug-resistant strains, in particular methicillin- and vancomycin-resistant strains that are endemic in hospital setting. In addition, community-acquired strains with reduced drug susceptibility or even resistant have been reported.[22,23] Antimicrobial resistance results in a delay in specific therapy, increasing the risk of disease chronification and of periprosthetic infection.[12]

Infections subsequent to stabilization of fractures or implants of joint prostheses are devastating complications difficult to treat. Prosthetic implants, which alters the environment, including local immunity, favors bacterial invasion. After the trauma, lesions of soft tissues, with decreased vascularization surrounding the fracture site and delayed healing, are important. As for bone and/or osteoarticular grafts, the success depends on biointegration between the metal implant and the bone by the formation of a tissue interface of host cells. However, the same phenomenon of adhesion and cell growth is promoted by some bacteria, in particular *S. aureus*, which, due to competition, impair biointegration. Early diagnosis and aggressive treatment of post-traumatic and periprosthetic bone infections with antibiotics, debridement, and/or stabilization of the internal fixation are essential for the success of treatment. Thus, it is common for surgeons to be faced with the dilemma between treatment of infection, which may require implant removal, and treatment of bone (fracture) or osteoarticular disease, which, in turn, requires implant maintenance.[13]

Post-arthroplasty infections are difficult to diagnose and treat and are associated with high morbidity and substantial costs. Advanced microbiological methods and novel imaging examinations have contributed to improvements in this therapy.[24] The incidence of post-arthroplasty infections is 1.5% to 2.5% for primary interventions; however, higher rates have been reported for revision surgeries (2% to 20%).[25] A consensual classification of periprosthetic infections has not been established yet, but they can be defined according to postoperative period in three types: early-onset, delayed-onset, or late-onset. Early manifestations are defined by the emergence of signs and symptoms within the first three post-arthroplasty months, although some authors limit this period to the first two to four weeks. Delayed-onset manifests between three months and two years, while late-onset evolves more than two years after surgery.[26-28] In early- and delayed-onset infections, the microorganisms can colonize the implant by direct inoculation during surgical intervention, while late-onset infections generally appear via the bloodstream.[27,29] *S. aureus* and *S. epidermidis* correspond to 65% of pathogens that cause these infections, although other agents may also reach the prosthetic surface.[28,30] Hence, procedures performed close to the genito-urinary and gastrointestinal tracts are the source of gram-negative bacilli, enterococci, and anaerobic organisms; similarly, dental and gum treatment are the source to the dissemination of S*treptococcus viridans*, *Peptococcus* spp. and *Peptostreptococcus* spp., as well as pyogenic skin infections, the classical source of *Streptococcus* spp.[31] Additionally, bone disease due to mycobacterial infections, multiple microbial infections, and infections caused by uncommon pathogens, such as *Candida* spp., *Brucella* spp., have been reported.[27,32,33]

Clinical-epidemiological profile of osteomyelitis in Brazil

Despite the importance of isolation and identification of microorganisms to determine antimicrobial treatment of bone infections, there are few systematic national studies on the etiological profile of these diseases. After an extensive review of publications in the Medline and SciELO databases, only nine articles published on this subject in Brazilian populations over the last 13 years were found. These works describe

specific clinical situations particular to each of the Orthopedics and Traumatology Services. Thus, standardization of a treatment protocol for osteomyelitis remains a challenge.

Table 2 summarizes published national data related to bone infections after exposed fractures or consequent to arthroplasty (knee and hip) and the main clinical-epidemiological factors

Table 2. Main clinical-epidemiological factors of bone infections after trauma and arthroplasty according to data from different Orthopedics and Traumatology Services in the state of São Paulo

Author (year)	n	Fracture/ Prosthesis	Period	Frequency	Risk factors	Infectious agent	Therapy
Lima *et al.* 2004	134	Exposed fractures of the lower limbs	02/1998 05/2000	40.3%	- Volume of transfused blood - ASA III - Immediate internal fixation of bone - Femur - Open wound	-	Surgical debridement and antimicrobial therapy
Muller. *et al* 2003	117	Exposed fractures Diverse bones	2000 2002	20.5%*	NE	NE**	Antimicrobial therapy and external fixation
Lima *et al.* 2001	46	Total hip arthroplasty	1993 1995	15.1%	Operative time greater than 140 minutes	*P. aeruginosa* Coagulase-negative staphylococci *Morganella morgani* *Acinetobacter calcoaceticus* *Staphylococcus* spp. *P. aeruginosa* *E. coli*	Surgical debridement
Rudelli *et al.* 2008	32	Total hip arthroplasty	1989 2000	¶	NE	*S. aureus* Coagulase-negative staphylococci *Enterococcus faecalis* *E. coli* *Peptostretococcus* spp. *Acinetobacter* spp. *Streptococcus mitis*	One-stage revision with bone graft Empiric and directed antibiotic therapy
Leonhardt *et al.* 2006	12	Total knee arthroplasty	2003 2004	8.3%	NE	Oxacillin-sensitive *S. aureus* ***	Revision of prosthesis in two stages, and after six months of spacer and antimicrobial therapy
Queiroz & Luzo 1996	250	Total knee arthroplasty	01/1991 06/1995	6%	NE	*S. aureus* *Enterobacter* spp *S. epidermidis* *Klebsiella* spp. *P. aeruginosa*	Arthroplasty, debridement and maintenance of the prosthesis, arthrodesis, resection of the prosthesis, use of cement with gentamicin and revision surgery

NE, not evaluated.
*Acute phase infection.
**Isolation of microorganisms at time of admittance, before surgical debridement.
***The only published data on sensitivity profile.
¶ All patients underwent one-stage revision of loose and infected hip arthroplasty.

involved, all of which were obtained in Orthopedics and Traumatology Services in the state of São Paulo. In general, *S. aureus* was described as an important etiological agent; however, the difference in national study designs makes comparison between prevalence of bone infection, associated risk factors, and different therapeutic approaches difficult. Only two studies referred to the frequency of post-fracture osteomyelitis, which ranged from 20.5%[15] to 40.3%[34] in different services. Lima *et al.*[34] reported the following risk factors: volume of transfused blood, ASA level III clinical classification, immediate internal fixation of the bone, femur fractures, and the presence of an open wound. The microbiological profile of infections was not described in these studies. In respect to hip arthroplasties, a single study reported the infection rate of around 15%,[35] higher than the percentage described for arthroplasties of the knee (6% to 8%) reported by two other groups.[36,37] As for risk factors in hip arthroplasties, operative times greater than 140 minutes were identified as significant.[35] Gram-positive cocci, with predominance of *S. aureus*, were the most commonly isolated microorganisms after arthroplasties of the knee and hip.[36-38] In a single study, coagulase-negative staphylococci, *Pseudomonas aeruginosa*, and *Acinetobacter calcoaceticus* were equally implicated as etiological agents of infection after hip arthroplasties.[35] In a different approach involving one-stage revision in 32 patients with loose and infected hip arthroplasties, Rudelli *et al.* (2008)[39] found coagulase-negative staphylococci as the mainly isolated bacteria. On the other hand, a great diversity of Gram-negative bacteria (eleven different species – totaling 31.5% of all the agents isolated) was described by Cabrita *et al.*[38] in infections after hip arthroplasties. For further information on bone infections data in Brazil, we do recommend two review articles on osteomyelitis diagnosis and treatment and also on infection following total knee joint arthroplasty by Lima & Zumiotti (1999)[40] and Lima *et al.* (2004),[41] respectively.

The availability of surgical techniques and leading-edge bone devices, combined with more accurate diagnosis has provided better treatment and an increased life expectancy of patients with osteoarticular and multiple-trauma diseases. In this regard, the incessant occurrence of bone infections is a motive of frustration for both surgeons and patients.[8] Among the causes of this lack of success is the insufficient evidence that supports efficacious antimicrobial therapies for osteomyelitis.[42] The choice of antibiotics, although limited by the sensitivity of etiological agents, should also be based on the choice of appropriate via of administration, safety of long-term use, and cost.[43] The heterogeneity among populations of patients and the multiplicity of clinical and surgical therapeutic options were also reported as complications in the reduction of bone infection rates.[39] Hence, only a multidisciplinary approach of orthopedic surgeons, infectologists, radiologists, and vascular and plastic surgeons, as well as rheumatologists will improve therapeutic outcomes.[3,24]

In conclusion, effort is necessary in order to stimulate systematic national studies in different Orthopedics and Traumatology Services to obtain a better consensus on preventive measures and therapies of bone infections.

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