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Research Article

Therapeutic Hematogenous Osteomyelitis in Children

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Abstract

Objective: To evaluate the results of surgical treatment based on the creation of several cortical holes and continuous irrigation with antibiotics in the treatment of hemorrhagic tibial osteomyelitis in children.

Materials and Methods: The analysis was performed on data collected from 268 patients (276 bones), from September 1994 to December 2014. The mean age at the time of surgery was 4 years and 5 months. Information on the diagnosis of osteomyelitis was collected such as clinical examination, plain radiography and ultrasound. Paraclinical tests including bacterial culture, white blood cell count, erythrocyte sedimentation rate and C-reactive. Osteomyelitis was classified into 3 stages: acute, intermediate and chronic osteomyelitis. Surgical techniques: Cortical bone fenestrations with continuous antibiotic irrigation for long bone; and debridement for flat bone.

Results: There were 268 patients (276 bones); 106 (39.6%) female and 162 (60.4%) male. Unilateral lesions were most common, with the left bone affected in 87 (32.5%) and the right bone in 173 (64.5%) patients. Both bones were affected in 8 (3.0%) patients. There were 284 bones, including Humerus 61 (21.5%), Femur 92 (32.4%), Tibia 114 (40.2%) were long bone; and Fibula 17 (5.9%) were flat bone. All patients were classified as having intermediate stage of osteomyelitis. Overall, we achieved good results in 215 tibiae (77.9%), fair results in 59 tibiae (21.4%) and poor results in 2 (0.7%) tibiae with progressive chronic osteomyelitis 1, and pathologic fracture 1.

Conclusion: Overall, all Intermediate Osteomyelitis, and surgical treatment of osteomyelitis of the bone is safe and effective. We suggest that this treatment method can be applied to osteomyelitis of the bones.

***Keywords**: Debridement; Osteomyelitis; Tibia; Infection; Children*

Introduction

Bone and etiology

Site of hematogenous osteomyelitis

Osteomyelitis is more common in children of all ages and is more common in developing countries (Figure 1). Osteomyelitis is an inflammation of the bone, usually caused by pyogenic bacteria, most commonly *Staphylococcus aureus*. Hematogenous osteomyelitis

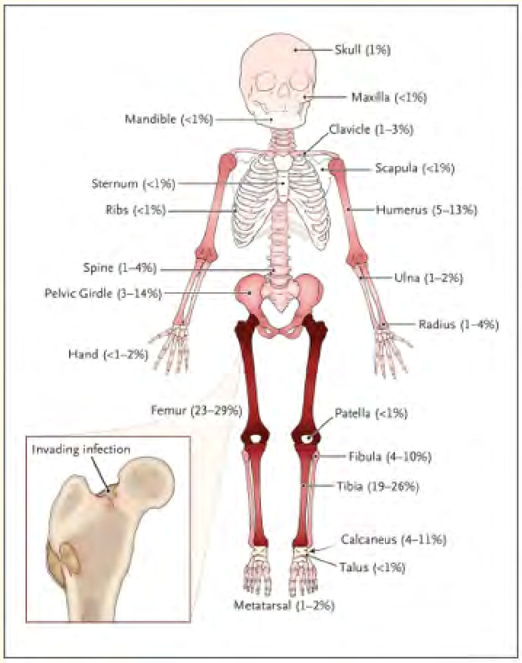

Figure 1: *Skeletal distribution of acute osteomyelitis in children. Osteomyelitis may affect any bone, with a predilection for the tubular bones of the arms and legs. Estimated percentages of all cases according to the data in Krogstad [1]; Gillespie and Mayo [2]; Peltola., et al. [3] and Dartnell., et al. [4] are shown. Darker shades of red denote a higher burden of infection.*

remains an important infection in children, with potential consequences for bone growth and function. Hematogenous osteomyelitis can be acquired hematogenously (mainly in young children), by direct infection, or from a nearby focus of infection (Figure 2).

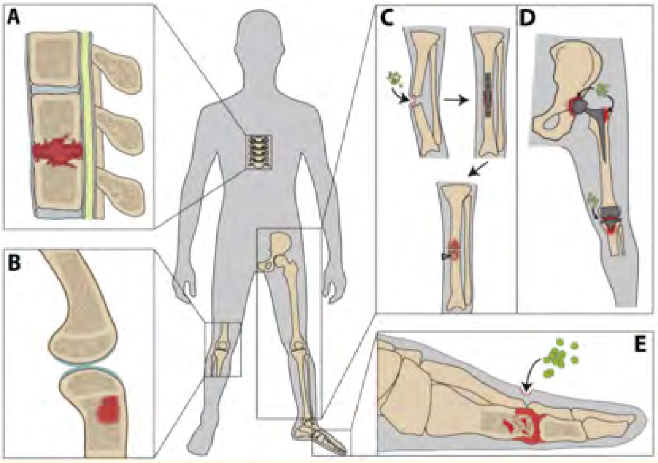

Figure 2: *A diagram showing three categories of osteomyelitis. (A and B) Primary hematogenous (blood borne) spread of bacteria mainly afflicts the vertebral bodies at all ages or the metaphysis of skeletally immature patients. (C and D) Contiguous bone infection is most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with prosthetic implants. (E) Vascular or neurologic disease associated osteomyelitis most commonly affects the lower extremity.*

Etiology

The characteristics of each type can be summarized as follows: (1) Primary hematogenous spread primarily affects the subchondral bone or vertebral body of skeletally immature patients of any age, although infection at other sites may occur [5]. (2) Contiguous infection typically spreads from the site of infection, most commonly by direct bacterial infection in open fractures or joint replacement surgery with orthopedic implants. Osteomyelitis associated with vascular or neurovascular compromise results from poor blood supply, diabetic wounds, loss of protective sensation, and immunosuppression, and typically affects the lower extremities (Figure 3).

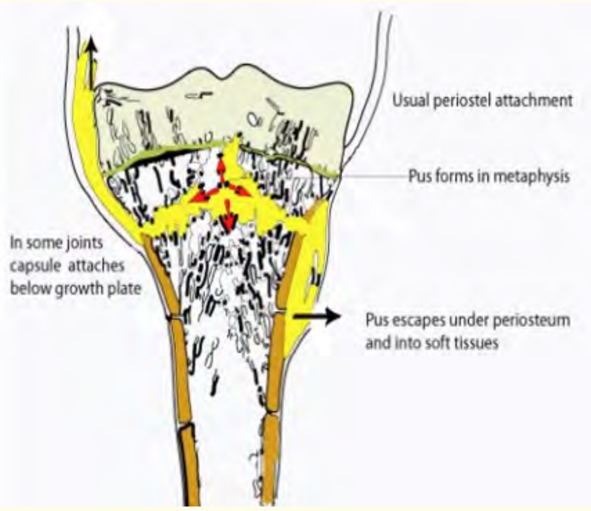

Figure 3: *Osteomyelitis originating from metaphysis.*

Historically, the mortality rate of osteomyelitis has been reported to be as high as 45%. Osteomyelitis in children occurs primarily because the blood supply may be compromised by trauma. Traditional surgical techniques (pus drainage) are associated with poor postoperative outcomes and a 5 - 45% risk of developing chronic osteomyelitis.

Pathophysiology of osteomyelitis

Causative factors

Staphylococcus aureus that invades the bone surface via the bloodstream or therapeutic route can easily adhere to soft tissue, bone, or metal implants. This can be achieved by binding to extracellular matrix (ECM) proteins via bacterial surface components that recognize adhesion matrix molecules, such as collagen-binding proteins and bone sialoprotein-binding proteins [5].

Herein, *S. aureus* employs multiple survival strategies to not be affected by immune cells and therapies (Figure 1A). Adherent *S. aureus* may multiply, aggregate, and form microcolonies, which are also known as staphylococcal abscess communities (SACs) (Figure 1D). SACs are not exclusively found in bone tissue; they have been observed in skin, kidney, renal, and brain tissues. In most cases, the SACs form the center of an abscess structure with surrounding fibrin deposits. Specifically, *S. aureus* can form fibrin by promoting polymerization of fibrinogen and secreting enzymes, such as coagulase and von Willebrand factor binding protein, which activate endogenous prothrombin and contribute to fibrin formation.

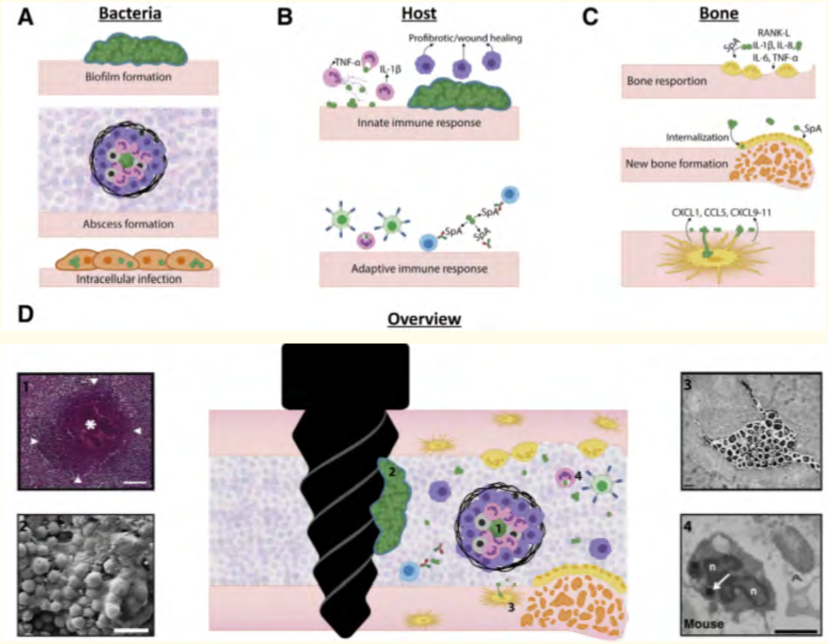

Figure 4: *A mechanistic illustration of the pathophysiology of osteomyelitis. A: Bacteria: survival strategies of Staphylococcus aureus in bone to circumvent immune cell responses and therapies are i) forming biofilm that contains an extracellular polymeric substance matrix, ii) growing as staphylococcal abscess communities (SACs) as part of an encapsulated abscess, or iii) performing intracellular colonization of host cells. B: Host: bacterial presence in bone initiates an influx of innate immune cells. During acute inflammation, polymorphonuclear cells (PMNs) predominate, and during chronic inflammation, macrophage numbers increase. PMNs secrete proinflammatory cytokines, including IL-1b and tumor necrosis factor (TNF)-a, and release neutrophil extracellular traps (NETs) to facilitate bacterial killing. Macrophages are skewed toward a wound healing and profibrotic phenotype. Adaptive immune responses include T- and B-cell responses. However, T-cell responses are skewed by S. aureus toward type 1 and type 17 helper T cell biased immune responses. Staphylococcus aureus protein A (SpA) binds to antibodies secreted by B cells and consequently blocks antibody-mediated phagocytosis. C: Bone: bacterial presence promotes i) host cells to secrete probone resorptive cytokines, causing, together with SpA binding, bone resorption by osteoclasts, ii) osteoblasts to form new bone because of internalization of the bacterium and SpA binding, and iii) secretion of the chemoattractants C-X-C motif chemokine ligand 1 (CXCL1) and C-C motif chemokine ligand 5 (CCL5) for PMN recruitment and CXCR3-binding chemokines CXCL9, CXCL10, and CXCL11 for T-lymphocyte recruitment by (invaded) osteocytes. D: An overview of the different osteomyelitis components accompanied by in vivo images of the following: 1, a staphylococcal abscess commu (SAC) (asterisk) surrounded by immune cells (arrowheads), as observed in a hematoxylin and eosin stained paraffin-embedded section containing an S. aureus infected murine femur 2, biofilm on a polyether ether ketone fixation plate imaged with scanning electron microscopy; 3, S. aureus within an osteocyte canaliculus; and 4, S. aureus bacterium (arrow) within a PMN, [6] both observed with transmission electron microscopy. Green cells, S. aureus; black strands, fibrous tissue; gray cells, dead cells; pink cells, PMNs; purple cells, macrophages; orange cells, generic cells; pink cell with purple/gray strands, PMNs undergoing NETosis; light green cells, T cells; blue cells, B cells; multinuclear yellow cells, osteoclasts; yellow cells, osteoblasts; elongated yellow cells, osteocytes. D: Image 1 reprinted from Brandt., et al. [7] with permission (Copyright 2018. The American Association of Immunologists, Inc.); image 2 reprinted from Inzana., et al. [8] with permission; image 3 reprinted from de Mesy Bentley., et al. [9] with permission; and image 4 reprinted from Horst., et al. [6] with permission. Images in AeC and the schematic in D were generated with BioRender (Toronto, ON, Canada). Scale bars: 100 mm (D, image 1); 2 mm (D, images 2 and 4); 1 mm (D, image 3). n, nucleus; RANK-L, receptor activator of NF-kB ligand.*

This fibrin network surrounding the bacterial SACs protects the bacteria from invasion and clearance by immune cells, such as PMNs, causing the immune cells to gather around the bacterial nidus (Figure 4D).

Staphylococcus aureus adhering to implanted devices or sequestra may form an even more complex structure known as a biofilm (Figure 4D). Bacteria in biofilms are less susceptible to antibiotics, because of several factors, including reduced oxygen levels and metabolism. Furthermore, *S. aureus* resident in biofilm may secrete the so-called extracellular polymeric substance matrix consisting of self-produced polysaccharides and proteins and possibly extracellular DNA from dead bacterial cells, forming a matrix that functions as a physical barrier to immune cell infiltration.

Besides clustering in SACs or into biofilm, *S. aureus* can also invade the osteocyte-lacuno canaliculi networks within bone (Figure 4D). Recently, invasion of *S. aureus* in the submicron channels buried deep within the dense mineral matrix of cortical bone has been discovered Invasion of *S. aureus* within the canalicular network could be a mechanism to promote persistence and chronic infection, with the potential to limit access to immune cells. This novel persistence mechanism was originally identified in a mouse model of implant-associated osteomyelitis, and was subsequently confirmed in a human *S. aureus* diabetic foot infection. This discovery is particularly concerning in the context of *S. aureus* osteomyelitis, as these canalicular networks may be impenetrable by immune cells, and bacteria can possibly survive in this space for a long period of time, using bone matrix as a nutrient source. However, this has not been proved yet.

As another defense mechanism, *S. aureus* has a wide range of toxins that target host cells. These toxins include exfoliative toxins, pore-forming toxins, and superantigens.

The superantigen toxic shock syndrome toxin 1 has been associated with bone infection. It has been shown that toxic shock syndrome toxin 1 can promote osteoclastogenesis and bone resorption activity of osteoclasts *in vitro*.

Also, pore-forming toxins have been linked to bone infection. *Staphylococcus aureus* pore-forming toxins can be subdivided into leukotoxins, hemolysin-a, hemolysin-b, and phenol-soluble modulins; and these proteins affect host cell membrane integrity. For phenol-soluble modulins, it has been demonstrated *in vitro* to have a cytotoxic effect on osteoblasts, whereas the hemolysin-a caused both osteoblast and osteoclast cell death *in vitro*. Hemolysin-b may be involved in phagosomal escape, as shown *in vitro* in PMNs, and *in vivo* it stimulated biofilm formation. Furthermore, human osteomyelitis patients infected with an *S. aureus* strain that can secrete the leukotoxin Panton-Valentine leucocidin had a more aggressive and more difficult to treat infection.

In addition, *S. aureus* can invade and survive intracellularly in professional phagocytes, as well as nonprofessional phagocytes (Figure 4D). *Staphylococcus aureus* triggers phagocytic internalization by expressing fibronectin-binding proteins (A and B), adhering to fibronectin, and connecting to a5b1 integrins on macrophages or neutrophils. After internalization, *S. aureus* evades cell death in these cells by persisting within vacuoles or by inhibiting phagolysosomal fusion. It can also infect and survive within non-professional phagocytes, such as primary human osteoblasts *in vitro*, mouse osteoclasts *in vitro* and *in vivo*, and human osteocytes *in vitro* and *ex vivo*. This intracellular persistence provides the pathogen with crucial protection needed against the onslaught of the immune system and antibiotic treatments. *Staphylococcus aureus* infected human osteoblasts may also mature into osteocytes and remain infected. To survive intracellularly, *S. aureus* frequently adopts a dormant small colony variant phenotype, characterized by slow growth and reduced metabolic activity. The numerous mechanisms by which *S. aureus* is able to survive intracellularly within the bone niche for long periods is a primary cause of chronic and recurrent osteomyelitis.

Host factors

The presence of bacteria in bone tissue triggers host responses, including innate immune responses driven primarily by polymorphonuclear neutrophils (PMNs), macrophages, and adaptive responses mediated by T cells, B cells, and pathogen-specific antibodies (Figure 1B). First, upon bacterial recognition, bone-resident macrophages [10], osteocytes, and osteoblasts are all capable of secreting chemoattractants that trigger immune cell influx to the site of infection. PMN influx in acute osteomyelitis occurs in both humans and rodent models of osteomyelitis. Inflammatory macrophages [myelocytic-associated protein 8 (MRP8)/MRP14 positive] and CD4 T cells, which are capable of activating PMNs, have also been observed in humans; and numerous necrotic immune cells are present in rodent models of osteomyelitis [6]. PMNs can effectively kill planktonic *S. aureus* through phagocytosis, oxidative burst, and antimicrobial peptide production, while secreting proinflammatory cytokines and chemokines, such as tumor necrosis factor (TNF)-α, IL-1b, CXCL2, CXCL3, and others, activating and recruiting PMNs, ultimately leading to pathogen clearance [11]. PMNs and macrophages also stimulate the host's direct defense response by forming neutrophil extracellular traps to trap bacteria, which will eventually be killed by immune cells. When the infection persists and becomes chronic, bacteria tend to form a biofilm phenotype, and the survival of PMNs is sharply reduced, as demonstrated in mice and observed in humans with chronic osteomyelitis. In humans, the majority of cells present at the site of chronic infection are wound-healing M2 macrophages (CD163 positive), accompanied by a small number of CD8 T cells and plasma cells. The predominant M2 macrophages are ineffective at phagocytizing bacteria within biofilms, and they tend to promote a fibrotic environment and wound-healing response, resulting in abscess formation during chronic osteomyelitis.

Adaptive immune responses to bone infection include both T-cell and B-cell responses. Unfortunately, pathogens such as *S. aureus* have evolved multiple mechanisms to evade these responses, resulting in chronic osteomyelitis. For example, in a porcine osteomyelitis infection model, it was observed that the antibody response against intracellular *S. aureus* in biofilms was skewed toward a type 1 and type 17 helper T cell-dominated immune response, which failed to effectively eliminate intracellular pathogens [12]. *Staphylococcus aureus* can also effectively manipulate B cells, affecting their survival and function through the secretion of staphylococcal protein A (SpA), which binds to the Fcg and Fab domains of some antibodies, blocking antibody-mediated phagocytosis and simultaneously inducing B cell proliferation and apoptosis. In addition, pathogen-specific antibodies produced by plasma cells and circulating plasma cells are often ineffective in protecting against chronic bone infections. Although further research is needed to fully understand this, it is possible that SpA secreted interfering antibodies against *S. aureus* do not provide protection against reinfection or chronic musculoskeletal infections, or that these antibodies are non-neutralizing. In fact, anti-*S. aureus* IgG responses against certain antigens can be fatal.

However, these antibody responses may be useful diagnostic and prognostic biomarkers for identifying orthopedic infections. Bacterial interactions with bone cells: Bone is a mineralized organic matrix containing osteocytes, osteoblasts, and osteoclasts.

All three bone cells are affected directly and indirectly by *S. aureus* (Figure 5).

Directly, SpA binds to the TNF-1 receptor on osteoblasts, leading to increased apoptosis and decreased osteoblast differentiation and calcium deposition. Furthermore, *S. aureus* internalization via integrin A/Bea5b1 binding to fibronectin affected osteoblast cell viability and activity. Both *S. aureus* internalization and SpA binding resulted in decreased bone formation and inhibited matrix mineralization.

In contrast, *S. aureus* infection increased periosteal bone formation by osteoblasts (as shown in rabbits) (Figure 5A) compared with uninfected controls (Figure 5B). Osteoclasts upregulate their bone resorption capacity due to activation of TNF and epidermal growth factor receptor via SpA secreted by *S. aureus*. This leads to the formation of resorption cavities and necrotic bone fragments, as observed in biopsies of human osteomyelitis patients (Figure 5C) and in *in vivo* osteomyelitis models [6] (Figure 5D). Indirectly, osteoclasts are activated and increase the bone resorption activity of osteoblasts, osteocytes, and PMNs. These cell types secrete NF-kB activator receptor

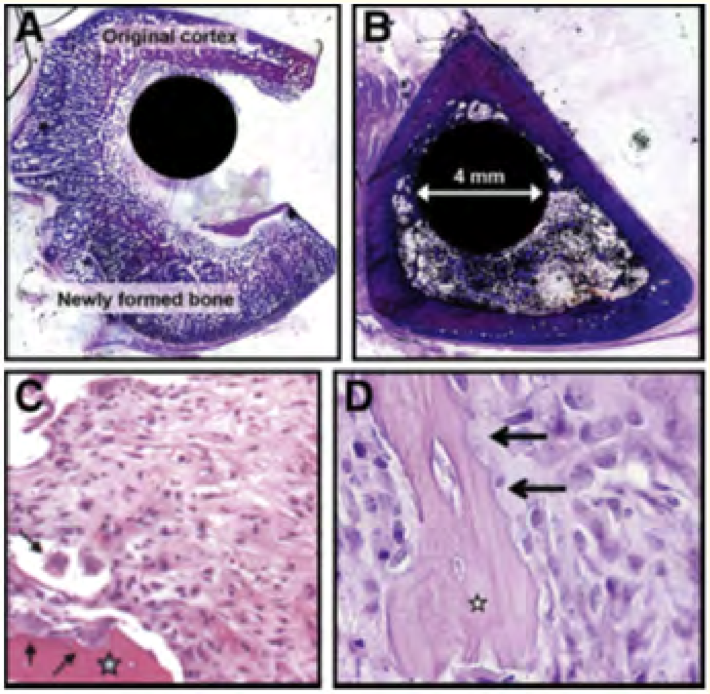

Figure 5: *Staphylococcus aureus infection has a dramatic impact on bone. A: Infection causes periosteal bone formation, as observed in methyl methacrylate sections of an infected rabbit tibia stained with methylene blue/basic fuchsin. B: No periosteal bone is formed in control tibia samples. C and D: Furthermore, infection results in osteonecrosis and osteolysis by osteoclasts (arrows) actively resorbing bone (stars), as shown in hematoxylin and eosin stained histologic sections from a paraffin-embedded human biopsy [14] (C) and mouse tibia (D) [6]. Panels A and B reprinted with permission from Mary Ann Liebert, Inc. [13]; panel C reprinted from Gaida., et al. [14] with permission; panel D reprinted from Horst., et al. [6] with permission. Original magnification: _200 (C); 40 (D).*

ligand (RANK-L), which promotes osteoclast formation and activates osteoclasts for bone resorption. Osteocytes do so in response to a neighboring osteoclast that has undergone apoptosis (e.g. due to *S. aureus* invasion of its crypts). Furthermore, osteoblasts upregulate RANK-L expression when SpA binds to the TNF-1 receptor and when intracellular bacteria do, while polymorphonuclear neutrophils (PMNs) upregulate RANK-L secretion via activation of toll-like receptor-4.

PMNs also promote osteoclastogenesis and bone resorption via osteoclast-mediated IL-8 secretion. Another factor contributing to osteoclastogenesis and osteoclast activity is a persistent inflammatory environment. This occurs initially through the secretion of pro-osteoclastogenic cytokines IL-6, TNF-α, and IL-1b by immune cells and osteoblasts, and later through hypoxia due to persistent inflammation.

An important role of osteoblasts is the maturation and maintenance of the mineralized matrix, which is accomplished through the expression of enzymes capable of reversibly removing minerals and remodeling the organic phase of the bone matrix, a process described as osteoblast osteolysis or periosteum remodeling. The involvement of this process in osteomyelitis is not yet well characterized, although activated matrix metalloproteinase expression has been observed in *S. aureus*-infected human osteoblasts, suggesting that osteoblast bone resorption is influenced by *S. aureus*. Another interesting function of osteoblasts is their potential role in recruiting immune cells. A recent study demonstrated that cultures of human osteoblasts exposed to *S. aureus* resulted in differential expression of over 1500 genes, including a strong induction of a large number of chemokines and cytokines. Although classical PMN chemoattractants, such as CXCL1 and chemokine ligand (C-C motif) 5, have been identified, CXC chemokine receptor 3 (CXCR3)-associated chemokines CXCL9, CXCL10, and CXCL11 are also highly expressed, suggesting the potential involvement of osteocytes in the adaptive immune response to bacterial infection by attracting cytotoxic and/or suppressor T lymphocyte subsets to infected sites.

Further studies on the role of osteocytes in this area would be of interest. Overall, *S. aureus* infection enhances osteoclast bone resorption (possibly osteoclast bone resorption), 36 and inhibits bone formation, resulting in overall bone tissue loss.

Current 3D *in vitro* infection models

In vitro 3D cell culture systems are becoming the standard in many areas of biology, including infectious disease research. 3D cell culture structures can be created using scaffold-based or scaffold-free methods (e.g. forced flotation or hanging drop methods). Because cells grow in a 3D environment that includes the ECM, cells in *in vitro* 3D culture models can have complex interactions not only with each other but also with the ECM. Therefore, cells in 3D cultures do not lose cell polarity, have improved viability [15], and have morphological characteristics similar to those observed *in vivo*.

Furthermore, an advantage of 3D cell culture models over animal models, including humanized mice, is that human cells and fluids can be used. This is of particular interest because *S. aureus* has some human-specific functions (e.g. staphylokinase has been shown to have less activity against mouse plasminogen than against human plasminogen). 3D models developed for other infections may contain relevant information for developing *in vitro* osteomyelitis models. Recent examples of 3D *in vitro* infection models include organoids, rotating wall vascular (RWV) bioreactors, collagen gel microcolonies, bacterial inks, human skin mimics, *ex vivo* models, microfluidic 3D models, and 3D osteomyelitis models. Figure 3 illustrates these 3D *in vitro* infection models.

Infected organoid cultures have been used to study host-microbe interactions with a variety of pathogens. Organoids are simplified versions of organs that grow in a matrix with appropriate environmental cues from single stem cells with their self-organizing capabilities. Figure 5A illustrates gastric organoid cultures with *Helicobacter pylori* infection. Gastric organoids are cultured from gastric stem cells, and this model has been used to study infection-induced changes in gastric epithelial cells. It has been shown that *H. pylori* infection causes upregulation of the NF-kB pathway in infected gastric organoids and subsequently increases IL-8, a neutrophil chemoattractant that promotes inflammation. In a more complex model, intestinal organoids derived from a human embryonic stem cell line have been used to simulate intestinal infection with *Escherichia coli*. Organoids infected with *E. coli* were then exposed to PMNs to thoroughly examine innate immune responses, such as the production of reactive oxygen species. Interestingly, *E. coli* infection resulted in PMN production of reactive oxygen species and PMN migration, but bacterial numbers were not reduced [16].

Another method for obtaining 3D organoid structures is to use the RWV bioreactor. Cells are first cultured in a monolayer and allowed to aggregate on a scaffold, such as ECM-coated microcarriers, and then transferred into the RWV bioreactor, or self-aggregate by transferring cells directly into the RWV bioreactor. In the RWV bioreactor, cells are subjected to low shear forces and gently fall along a limited trajectory, first promoting 3D cell aggregation and then differentiation. To study host-pathogen interactions with the RWV bioreactor, 3D aggregates have been formed for tissues such as the lung, bladder, and intestine. 4D intestinal aggregates were used to study *Salmonella enterica serovar typhimurium* infection (Figure 6B). In this study, 3D intestinal aggregates were created using the RWV bioreactor or a monolayer of small intestinal epithelial cells (commonly used) that were infected with *S. enterica serovar typhimurium*. *Salmonella* was less able to adhere to and invade the 3D intestinal aggregates than the monolayer of cells. The results showed that the 3D intestinal aggregates more accurately mimicked the *in vivo* environment, where most *S. enterica serovar typhimurium* remained extracellular (Figure 6).

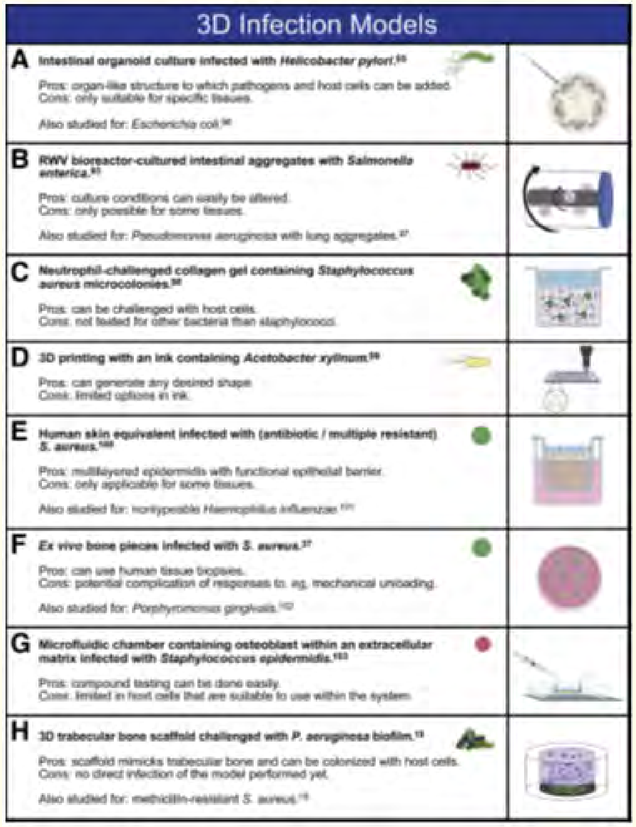

Figure 6A-6H: *Mode infection.*

This database data is extracted directly from the electronic medical record action has a data use agreement. Encounters may include pharmacy, clinical and microbiology, admission and billing information from affiliated patient care locations. All admissions, laboratory orders and specimens are date and time stamped, providing a temporal relationship between treatment patterns and clinical information.

Children under the age of 18 years diagnosed with acute osteomyelitis or chronic osteomyelitis in 2014 were eligible for analysis.

Aim of the Study

The aim of the study was to evaluate the clinical and paraclinical outcomes and treatment outcomes of two techniques Cortical bone fenestrations with continuous antibiotic irrigation and debridement for intermediate hematogenous osteomyelitis in children.

Materials and Methods

A retrospective study was performed to evaluate the results of surgical techniques performed between September 2004 and December 2019 on 276 patients (284 bones, including: Humerus 61 (21.5%), Femur 92 (32.4%), Tibia 114 (40.2%), Fibula 17 (5.9%) with hematogenous tibial osteomyelitis. The diagnosis of osteomyelitis was established based on the corresponding symptoms and signs and confirmed by positive culture results (bone aspiration or blood culture) and imaging tests. All patients with conditions associated with pathological tibial fracture, septic arthritis, pericarditis, pneumonia or persistent inflammatory syndrome were excluded from the list of patients analyzed.

The study was approved by the Ethics Review Committee of our Institute and was conducted according to the principles of the Declaration of Helsinki.

Clinical features

The clinical presentation of nonhematogenous osteomyelitis varies and symptoms are often nonspecific. Signs and symptoms common to all subtypes may include pain, edema, and erythema.

Figure 7: *Swelling leg with tibia osteomyelitis.*

Acute osteomyelitis may present with a more rapid onset of symptoms (development over days) and is more likely to be associated with fever (Figure 7). Systemic symptoms are not common in chronic osteomyelitis, and the presence of fistulous tracts from skin to bone is diagnostic. Long-standing, nonhealing ulcers and nonhealing fractures may also be associated with chronic osteomyelitis.

Patients with diabetic neuropathy are at higher risk of developing osteomyelitis secondary to local spread from diabetic foot infections and unrecognized wounds. Smoking increases the risk of osteomyelitis from diabetic foot infections and healing fractures. Peripheral vascular disease and poorly healing wounds (e.g. decubitus ulcers) are more likely to lead to bone inflammation. Osteomyelitis secondary to diabetic foot ulcers can be difficult to diagnose given chronic changes from vascular insufficiency and ischemia.

Hematogenous osteomyelitis often presents similarly to nonhematogenous disease. The most common form of hematogenous osteomyelitis is vertebral; patients often have back or neck pain and muscle tenderness, sometimes followed by fever. Hematogenous osteomyelitis may also occur in the sternoclavicular, pelvic, and long bones. When hematogenous osteomyelitis affects prepubertal children, it typically occurs in the metaphysis of long bones adjacent to growth plates, with a predilection for the tibia and femur.

Diagnosis

A diagnosis of osteomyelitis should be considered in any patient with acute onset or progressive worsening of musculoskeletal pain accompanied by constitutional symptoms such as fever, malaise, lethargy, and irritability. Constitutional symptoms do not always occur in adults, especially in the setting of immunocompromise. The index of suspicion for osteomyelitis should be higher in patients with underlying conditions, including poorly controlled diabetes mellitus, neuropathy, peripheral vascular disease, chronic or ulcerated wounds, history of recent trauma, sickle cell disease, history of implanted orthopedic hardware, or a history or suspicion of intravenous drug use. A dedicated physical examination can increase the likelihood of diagnosing osteomyelitis if findings include erythema, soft tissue infection, bony tenderness, joint effusion, decreased range of motion, or exposed bone. The probe-to-bone test may be useful to rule out diabetic foot osteomyelitis in low-risk patients.

The differential diagnosis of osteomyelitis includes soft tissue infection, gout, Charcot arthropathy, fracture, malignancy, bursitis, osteonecrosis, sickle cell vasoocclusive pain crisis, and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). Uncertain clinical diagnosis should prompt further workup that includes laboratory evaluation and imaging. Definitive diagnosis is made with a positive culture from biopsy of the affected bony structure. Polymerase chain reaction testing may help in the rapid diagnosis of organisms or for cultures taken after antibiotic therapy. Bone biopsy remains the diagnostic standard but is not always feasible. Some evidence suggests that biopsy should be reserved only for select cases because the results may not lead to treatment alterations.

Laboratory evaluation

Initial laboratory evaluation should include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, and blood cultures. Leukocytosis may be present in acute osteomyelitis, but it can be absent in chronic osteomyelitis. There is some evidence that thrombocytosis may positively predict osteomyelitis in patients with chronic leg ulcers. If inflammatory markers are elevated, they can be trended for clinical correlation. Positive blood cultures in association with radiographic.

Blood culture

This test detects and identifies bacteria present in the blood that may be causing osteomyelitis. A positive blood culture can provide evidence of the specific bacteria causing the bone infection, allowing healthcare providers to choose the most appropriate antibiotic therapy. This is especially useful when the infection has spread throughout the body or when the causative agent needs to be identified for targeted therapy. Incidence of osteomyelitis may prevent the need for a more invasive bone biopsy.

Radiographic features

MRI is most accurate in detecting osteomyelitis with a sensitivity of 90% and a specificity of ~80%. In some cases, imaging features are specific to a particular area or type of infection, e.g.:

- Subperiosteal abscess
- Brodie abscess
- Pott's cyst
- Garré's fibrosing osteomyelitis.

The following are general features of osteomyelitis

Plain radiograph

The earliest changes are seen in the adjacent soft tissues +/- the muscle border with swelling and loss or blurring of normal fat layers. Effusion may be seen in adjacent joints.

In general, osteomyelitis must extend at least 1 cm and cause a ~40% (range 30-50%) reduction in bone mineral content to produce noticeable changes on plain radiographs. Initial findings may be subtle and changes may not be apparent until 5 to 7 days after onset in children and 10 to 14 days in adults. On radiographs after this period, several changes may be noted:

- Localised osteoporosis
- Periosteal reaction/thickening (periostitis): variable; may be aggressive, including Codman triangles
- Localised osteolysis or loss of cortical bone
- Endosteal scalloping
- Loss of trabecular bone architecture

- New bone fusions
- Eventually peripheral sclerosis.

In chronic or untreated cases, chronic osteomyelitis with characteristic imaging features may develop.

Ultrasound

Although ultrasound is a rapid and cost-effective soft tissue examination and can guide drainage of soft tissue inflammation, it has little role in the direct assessment of osteomyelitis because it cannot visualize the bone.

However, ultrasound has a role in the evaluation of soft tissues and joints adjacent to infected bones, as it can be used to visualize soft tissue abscesses, cellulitis, subperiosteal foci, and joint effusions.

Ultrasound is also useful in the evaluation of extra-osseous components of orthopedic devices, as it is not affected by metal artifacts.

CT

CT is superior to both MRI and plain radiography in delineating bony boundaries and identifying the mandible or capsule. The characteristics of CT are similar to plain radiography. The overall sensitivity and specificity of CT are low, even in chronic osteomyelitis, and according to one study, were 67% and 50%, respectively.

Intravenous contrast allows CT to differentiate between different tissue types and to delineate abscesses, but is inferior to MRI in this respect.

Some CT features include:

- Blurring of fat planes
- Increased density of fatty marrow
- Periosteal reaction
- Cortical erosion/destruction
- Jawbone, capsule, and gas in chronic osteomyelitis.

Some limitations of CT include:

- Inability to accurately detect marrow edema; therefore, a normal CT scan does not exclude early osteomyelitis.
- Reduced image quality due to banding artifacts in the presence of metal implants.

MRI

MRI is the most sensitive and specific modality, and can identify soft tissue/joint complications. Bone marrow edema is the earliest sign of acute osteomyelitis seen on MRI and can be detected as early as 1 to 2 days after the onset of infection. Low T1 signal and high signal on synovial fluid-sensitive sequences are characteristic signs of osteomyelitis on MRI.

- T1:
- Central component has intermediate to low signal.
- Surrounding bone marrow has lower than normal signal due to edema.

- Destruction of the bone cortex.
- T2: High bone marrow signal.
- T1 C+ (Gd): Postcontrast hyperintensity of bone marrow, abscess margins, periosteum, and adjacent soft tissues.

When there is heterogeneous bone marrow signal change (i.e. high signal on synovial fluid-sensitive sequences but normal T1 signal), the stronger the signal on synovial fluid-sensitive sequences (i.e. similar to synovial fluid signal), the higher the likelihood of osteomyelitis occurring or developing later.

Nuclear medicine

A number of techniques can be used to detect foci of osteomyelitis. These include:

- **Bone scintigraphy (Tc-99m):** Increased osteoblast activity leads to increased tracer uptake in surrounding bone, often on both delayed imaging and MRI. This technique is highly sensitive but not specific (Figure 8).

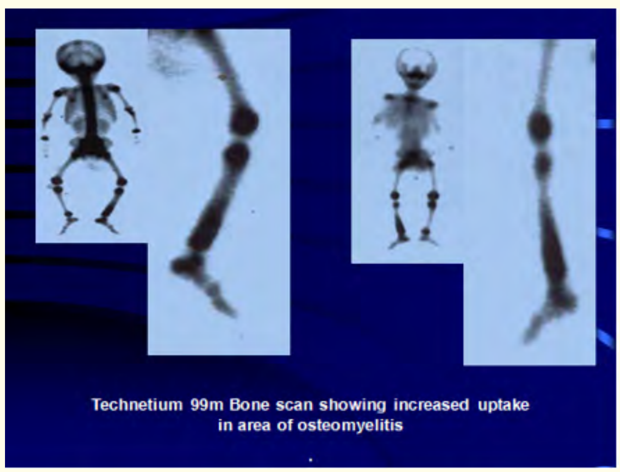

Figure 8: *Technetium 99m bone scan showing increased uptake in area of osteomyelitis.*

Indium-111 leukocyte scintigraphy

May be useful in:

- Diabetic osteomyelitis, especially when combined with Tc-99m-phosphonate imaging; However, MRI is now often used in conjunction with plain films.
- Orthopedic implants.
- Vertebral osteomyelitis (Ga-67 is best).
- Bedridden ulcers with potential risk of osteomyelitis (In-111 with Tc-99m-phosphonate).

Gallium-67 scintigraphy

- Gallium radiolabelled with transferrin, which leaks from the blood into areas of inflammation, shows increased isotope uptake in infection, sterile inflammation and malignancy.

- Imaging is usually performed 18 to 72 hours after injection and is often performed in conjunction with radionuclide bone scans.
- A difficulty with gallium is that it does not show bone detail well and may not differentiate well between bone and adjacent soft tissue inflammation.
- Gallium CT scans can detect abnormal deposits in patients with active osteomyelitis when technetium CT scans show reduced activity (lesions) "cold") or may be functional.
- Gallium accumulation may correlate more closely with inflammatory activity in osteomyelitis than technetium uptake.

PET-CT

PET-CT systems are relatively new techniques in use. FDG-PET may have the highest diagnostic accuracy in confirming or excluding chronic osteomyelitis compared to bone scan, magnetic resonance imaging (MRI), or leukocyte tomography. It is also considered superior to leukocyte tomography in detecting chronic osteomyelitis in the axial skeleton.

Classification

There are several classification systems for osteomyelitis. In general, there are three main classification systems including: the classification according to the sequence of symptoms, the Lew and Waldvogel classification, and the Cierny and Mader classification. Osteomyelitis can be classified according to the sequence of symptoms into acute, subacute (subdivided into the Glendhill and Robert., *et al*. system), and chronic. Chronic osteomyelitis can be divided into the Lew and Waldvogel classification system and the Cierny and Mader classification system. Osteomyelitis can be classified according to the Lew and Waldvogel system based on the duration and mechanism of infection into 3 subtypes: hematogenous osteomyelitis, adjacent fossa osteomyelitis, and secondary osteomyelitis due to vascular insufficiency. Osteomyelitis can be classified according to the Cierny and Mader classification system based on the anatomy of the bone infection (4 stages) and the physiology of the host (3 levels of injury).

There are several systems for classifying osteomyelitis:

- Osteomyelitis can be classified according to the chronological sequence of symptoms into acute, subacute (subdivided into the Glendhill and Robert., *et al*. systems) and chronic.
- Lew and Waldvogel classified osteomyelitis according to the timing and mechanism of infection (traditional classification) [17].
- Cierny and Mader classified osteomyelitis according to the anatomy of bone infection and host physiology [18].
- The Cierny and Mader system provides treatment guidelines.

Classification based on the chronological sequence of symptoms

- Acute osteomyelitis: Osteomyelitis is classified as acute if the duration of illness is less than 2 weeks.
- Subacute: Subacute hematogenous osteomyelitis has a more insidious onset and is asymptomatic, making the diagnosis of this disorder difficult. Diagnosis is often delayed by more than 2 weeks.

II	Metaphyseal radiolucencies with cortical erosion	--
III	Cortical hyperostosis in diaphysis; no onion skin reaction	Localized cortical periosteal reaction
IV	Subperiosteal new bone and onion skin layering	Onion skin periosteal reaction
V	--	Central radiolucency in epiphysis
VI	--	Destructive process involving vertebral body

Table A

- Chronic osteomyelitis: Chronic osteomyelitis is defined as persistent pain, erythema, or swelling, sometimes in association with a draining sinus tract that mostly lasts for more than 4 weeks.

The following table describes the classification schemes for chronic osteomyelitis.

Lew and Waldvogel etiologic system

Mechanism of Infection	Description
Hematogenous osteomyelitis	Osteomyelitis develops after bacteremia
Contiguous-focus osteomyelitis	Direct inoculation of bone via trauma/fracture, surgery, prosthetic devices, or spread from soft tissue
Osteomyelitis secondary to vascular insufficiency	Reduced blood supply, usually in diabetic patients

Table B

Cierny and Mader staging system

Classification		Description
Anatomic Type	Stage 1	Medullary osteomyelitis: infection confined to the intramedullary bone surfaces
	Stage 2	Superficial osteomyelitis: true contiguous infection (bone surface undergoes necrosis at the base of a soft tissue wound)
	Stage 3	Localized osteomyelitis: full-thickness, cortical sequestration
	Stage 4	Diffuse osteomyelitis: through-and-through process requiring intercalary reconstruction of bone
Physiological Class	A Host	Normal physiological, metabolic, and immunologic states
	B Host	Local compromise, systemic compromise, or both
	C Host	Morbidity of treatment is worse than disease

Table C

Before surgery in the surgical setting, information on the diagnosis of osteomyelitis can be easily gathered based on age, gender, medical history, time of onset, physical examination, and various imaging modalities. Patients with tibial osteomyelitis will complain of fever, chills, malaise, and vague leg pain. On examination, findings may include swelling, erythema, tenderness, and decreased range of motion. Laboratory tests should include bacterial culture (biopsy or aspiration), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels measured at admission and postoperatively at 1 and 6 weeks, and results at 3 months, 6 months, and 12 months are collected for analysis. Radiographic imaging should begin with plain radiographs and ultrasound [19] (Figure 9 and 10).

Postoperatively, patients were treated with intravenous (i.v.) antibiotics for 2 weeks and oral antibiotics for 4 weeks. The total duration of antibiotic treatment was 6 weeks.

Figure 9: *Technetium 99 m bone scan showing increased uptake in the area of osteomyelitis.*

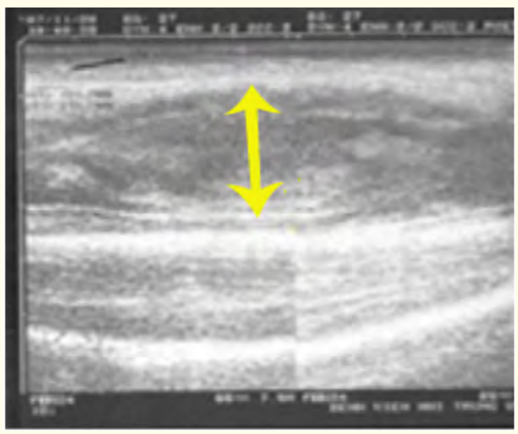

Figure 10: *Ultrasonography, subperiosteal pus on day 6 after disease onset.*

Osteomyelitis was divided into 3 stages: (1) Acute osteomyelitis, which develops within less than 3 days of the onset of the disease; (2) Intermediate osteomyelitis, which develops within less than 30 days; and (3) Chronic osteomyelitis, which develops over more than a month and involves the sinus or jawbone; with the presentation of each type based on the time of disease onset (i.e., infection or trauma).

One surgeon (the author) performed all surgeries.

Surgical procedure

Cortical bone fenestrations with continuous antibiotic irrigation

To perform the Schlumpf R anterior approach [20], the patient was placed supine with a pad under the affected hip to rotate the leg slightly inward. Make a 10-15 cm transverse incision parallel to the tibial crest (Figure 8A). Reflect the skin and periosteum in a single layer to expose the bone medially. Avoid elevating the entire soft tissue medially and laterally as this may compromise the blood supply to the bone if the bone is overexposed.

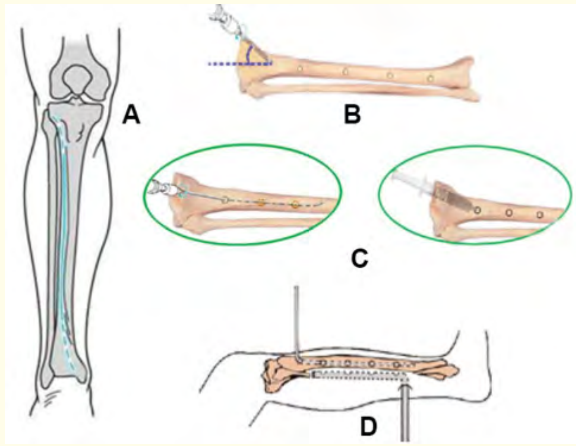

Figure 11A-11D: *A: Skin incision; B: Use hand saw to create some holes in cortical bone; C: Performing lavage of tibial medullary canal; D: Place system of irrigation.*

Surgical steps: (1) Using a hand drill with a 2.5 mm drill bit or a 2.5 mm Kirschner wire, make the first hole in the metaphysis and the midline of the anterior tubercle and the lower border of the tibia (or the distal tibial metaphysis if distal tibial osteomyelitis is present). The drill bit is 30° oblique to the tibial axis, thus allowing access to the medullary canal of the tibia (Figure 11B). Cultures and biopsies are taken from the medullary canal; To make several cortical holes in the anterolateral tibia with a drill bit or Kirschner wire, the distance between holes is approximately 1 inch (Figure 11B); Avoid drilling through the opposite cortical bone and only make holes in the exposed area of the tibial cortex due to periosteum necrosis; (2) Root canal curettage: use a slightly bent Kirschner wire (about 20°) at the wire point (Figure 11C), insert the curved point of the KW into the first hole and combine pushing down and gently rotating the KW starting from the first hole to the distal canal, starting with the Kirschner wire starting from a diameter of 2.0-2.5 and then 3.0 mm; then remove the Kirschner wire. Use a syringe to inject saline solution into some holes. Check the saline solution according to the holes (Figure 11C); (3) Set up the irrigation system: insert an 8 Fr catheter (Figure 11A and 8D) into the canal from the first hole to the distal canal of the tibia. Place a 16 Fr drainage tube at the lower border of the tibia to bring it out (Figure 10B and 10D); Coagulate all sources of bleeding to stop bleeding completely and close the skin and skin puncture wound, place the non-walking cast on the operating table with the knee slightly flexed and the ankle neutral, place the cast from the mid-thigh to the toes. Closely monitor the perfusion system and irrigation system.

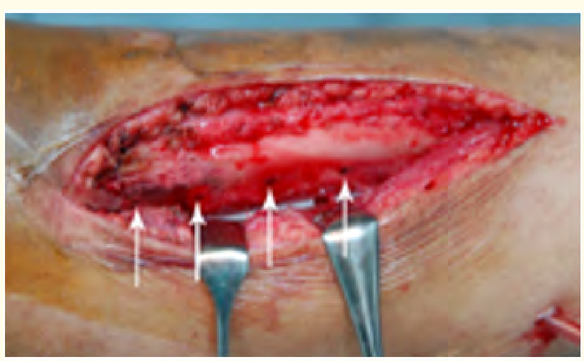

Figure 12: *Some holes were created in anterolateral cortical tibia.*

The irrigation with antibiotics: The system of infusion with saline solution 0.9%-2.000 ml and Gentamycin 80 mg per day for 7 days (Figure 12 and 13).

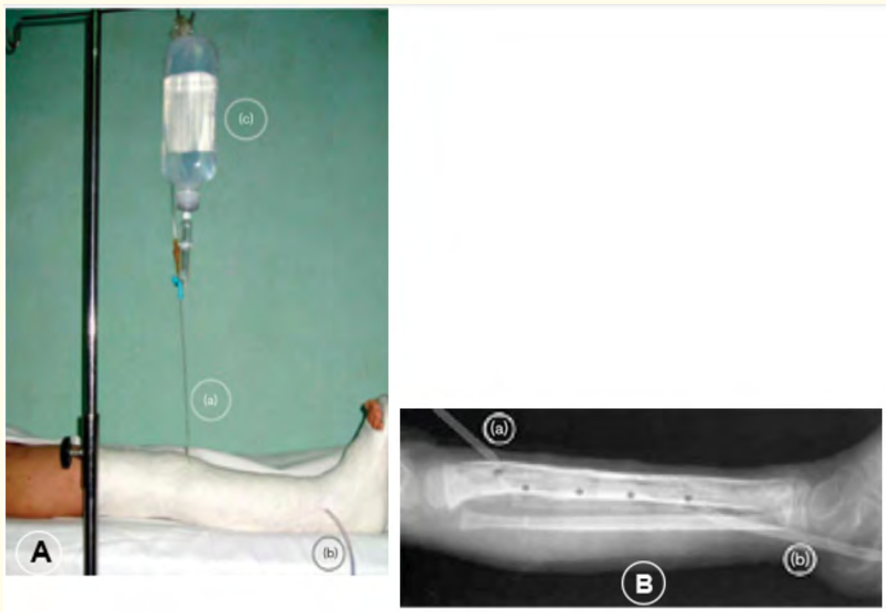

Figure 13A and 13B: *A: System of irrigation with gentamycin (a, catheter with a 8 Fr, b, drainage tube with a 16 Fr and it is connected with vacuum-associated closure, c, the irrigating solution). B: System of irrigation, (a) catheter was placed in medullary canal and (b) drainage tube was placed at the inferior border of the tibia.*

After operation

At day 8 after surgery, catheter and drainage-tube ware removed.

At 6 weeks after surgery, the non-walking cast was removed. The cast is then converted into a long walking cast, and progressive weight-bearing with crutches is allowed the next 6 weeks.

Follow-up: Patients were re-examined at 3 weeks, 6 weeks, 3 months, 6 months, 1 year, and afterwards every year. All patients were followed up to clinical, laboratory or radiographic

The criteria used for assessing the results of operation

	Restriction of movement of joint	Deformity of the limb	Pathological fracture	Discrepancy	Development of chronic osteo-myelitis	Addition of operation
Good	No	≤ 5°	No	≤ 2 cm	No	No
Fair	Moderate	> 5° - ≤ 20°	No	> 2 cm - ≤ 3 cm	No	No
Poor	Complete	> 20°	Yes	> 3 cm	Yes	Yes

Table 1: *The criteria used for assessing the results of operation.*

Results

From September 2004 to December 2019, there were 268 patients, 106 (39.6%) females and 162 (60.4%) males; 276 bones, Include: Humerus 61 (21.5%), Femur 92 (32.4%), Tibia 114 (40.2%), Fibula 17 (5.9%) with hematogenous osteomyelitis were operated. All diagnosis of osteomyelitis in patients was established based on compatible symptoms and signs and confirmed by positive culture (bone aspiration or blood culture) and imaging studies.

The median duration of symptoms before admission was 5 days (range, 4 to 28 days) for the patients with hematogenous osteomyelitis.

All patients were classified as the mediate stage.

The average age at the time of the operation was 4 years and 5 months (range: aged 22 days to 13 years, 7 months). There were 106 (39.6%) females and 162 (60.4%) males. Unilateral involvement was most common, with the left tibia affected in 87 (32.5%) patients, and the right in 173 (64.5%). Both tibiae were involved in 8 (3.0%) patients.

History of trauma in 37 (13.8%) children.

The most frequent findings on admission were as follow: localized pain (89.6%), tenderness (85.1%), swelling (100%). Other signs included decreased range of motion at the adjacent joint (49.7%), erythema (79.8%), fever (100%) and the average temperature at admission was 38.2°C (range, 37.8°C - 40.6°C).

The number of holes were created in the cortical bone: 3 holes in 15 (5.4%) tibiae, 4 holes in 252 (91.3%) tibiae, and 5 holes in 9 (3.3%) tibiae.

Laboratory characteristics

Characteristic laboratory on the day of admission: ESR: 54 (32-66); CRP: 35 (24-41); WBC: 22.200 (19.100-23.900); Neutrophil: 89 (84-95).

Characteristic	Postoperatively							
	1 day	5 days	7 days	3 weeks	6 weeks	3 months	6 moths	12 months
ESR (mm/h)	51 (32-65)	39 (30-43)	27 (23-31)	13 (10-15)	11(9-14)	9 (7-13)	7 (5-12)	7 (6-12)
CRP (mg/L)	25 (21-32)	18 (14-20)	12 (10-14)	11 (9-13)	11 (9-10)	8 (6-9)	7 (5-8)	5 (4-9)
WBC (cells/KL)	21,500 (19,200-23,600)	19,600 (16,500-21,300)	16,700 (14,600-18,100)	13,400 (11,300-15,600)	12,300 (11,600-14,500)	9,500 (7,600-14,100)	8,200 (7,100-9,600)	8,100 (6,900-9,900)
Neutrophils, %	87 (86-95)	85 (84-93)	81 (79-84)	80 (75-82)	79 (78-81)	77 (72-80)	75 (67-80)	74 (62-79)

Table 2: *Postoperative characteristics laboratory.*

(Normal characteristic laboratory: ESR: < 10 mm/h; CRP: < 10 mg/L; WBC: < 11.000; Neutrophil: < 60%).

Laboratory data included admission and postoperative discharge in table 2 as white blood cell counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Postoperatively, on the first day, ESR was elevated in 100%, CRP was elevated in 100%, WBC was elevated in 100% of cases. Postoperative on the third weeks, ESR was elevated in 45%, CRP was normal in 100%, WBC was elevated in 57% of cases. Postoperatively, ESR was elevated initially in 100% of the cases on the first day, the mean value was 51 mm/h, after this the levels slowly returned to normal in approximately 3 weeks. CRP was elevated (24-41 mg/L) at the time of admission, the mean value being 35 mg/L, and the decrease was very rapid, normal values being reached within a week. The WBC count was (mean, 21.500), the decrease was very slow and after 3 weeks WBC count was (mean, 13,400). There were 2 patients developed chronic osteomyelitis, after operation on 3 months with WBC count: 13,500 and 14.100 cells/KL; Neutrophils: 75% and 80%; ESR: 12 and 13 mm/h; CRP 11 and 12 mg/L.

Radiography

One or more plain radiographs were performed on 268 bone (276 Patients) patients with hematogenous osteomyelitis before or during admission. Most were performed on the day of admission (range, 4 - 28 days before admission) as shown in table 3.

Characteristic	Xray on the day of admission			
	4-7 days	8-15 days	16-21 days	22-30 days
Soft tissue swelling	69 (100%)	76 (100%)	115 (100%)	16 (100%)
Irregularity of the bone	25 (36.2%)	12 (15.8%)	115 (100%)	16 (100%)
Decreased bone density	12 (17.4%)	48 (63.2%)	115 (100%)	16 (100%)
Periosteal reaction		16 (21.1%)	94 (81.7%)	16 (100%)
	69	76	115	16

Table 3: *Characteristic Xray on the day of admission.*

Before 15 days, some abnormalities were recognized as irregularity of the bone in 37 of 145 (25.5%) tibiae, decreased bone density in 60 of 145 (41.4%) tibiae (cf. figure 3), soft tissue swelling occurred in all patients (100%) (cf. figure 5), and a periosteal reaction in 16 of 145 (11.0%) cases (cf. figure 4 and 5).

Blood cultures were performed in 276 patients and were positive in 39.6% (106/268). 34 patients had received antibiotics before their cultures being drawn, 3 of 34 (8.8%) cases grew an organism. The most commonly cultured organism was *S. aureus*, identified in 89 (83.9%) of the 106 positive cultures, followed by *S. pneumonia* in 6 (7.6%) patients, H. influenza type b in 6 (5.7%) cases and *Streptococcus pyogenes* in 3 (2.8%).

Other cultures obtained included needle bone aspiration or biopsies and were positive in 81.5% (225/276); *S. aureus* was the most common organism identified, being cultured from 192 (85.3%) of the 225 positive bone specimens. Followed by *S. pneumonia* in 9 (4.0%), and *Streptococcus pyogenes* in 7 (3.1%), *Citrobacter* in 6 (2.7%), *H. influenza* type b in 5 (2.2%), and *Proteus mirabilis* in 6 (2.7%) cases.

The average length of intravenous antibiotic treatment was 14 days (range, 13-16 days); for oral antibiotics it was 30 days (range, 29-32 days); and the average total antibiotic treatment was 44 days (range, 41-46 days). The most common antibiotics used included: Lincomycin, methicillin, cloxacillin, and gentamycin.

Follow up

The average duration of follow-up was 8 years, 9 months (range: 3 years, 6 months to 18 years, 4 months).

Long-term follow-up showed Good results in 77.9% (208 bone) (Figure 14), Fair results in 21.4% (58 bones) (Figure 15) and pathologic fracture on 1 (Figure 16), there were no other complications in these present.

Figure 14A and 14B: *Pre/postoperative on good result on 12 years and 3 months.*

Figure 15: *A-B: Pre/postoperative on fair result on 3 years and 6 months.*

Discussion

Nutritional regimen

We agree with the view of Saavedra-Lozano., *et al.* [21] that risk factors for worse outcomes in children with acute osteomyelitis are age, antibiotic treatment, number of days with symptoms before admission, leukocytosis and neutrophilia, inflammatory parameters (CRP and ESR), and anemia on admission. Immunocompetence is closely related to nutritional regimen and affects postoperative outcomes

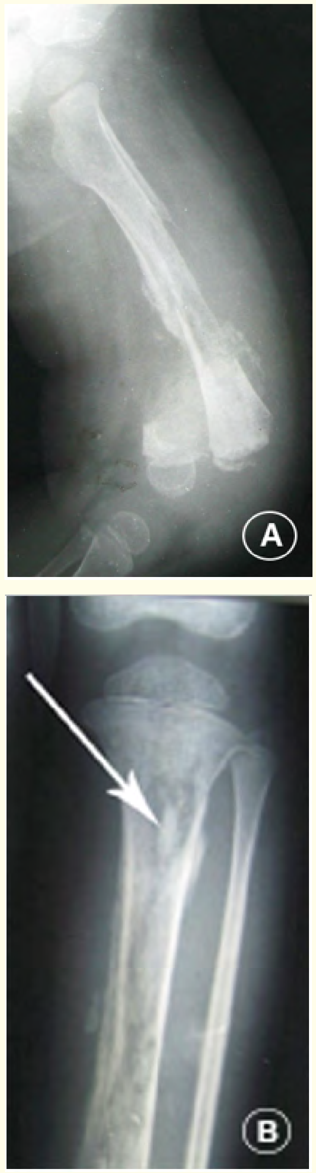

Figure 16A and 16B: *Poor results. A: Pathologic fracture on postoperative 15 months;*

B: Chronic osteomyelitis on postoperative 12 months.

[21]. There were 105 of 376 (27.9%) children with total blood protein less than 60 g/l, and 121 of 376 (32.2%) children with blood hemoglobin less than 10 g/l, requiring protein or blood transfusion.

Pathogenesis and definition

The pathological definition of osteomyelitis is inflammation of the bone and bone marrow caused by bacterial infection.

Chronic osteomyelitis has traditionally been defined as symptoms lasting less than 2 weeks, although the organisms and outcomes appear to be similar in patients with symptoms lasting up to 4 weeks. In contrast, chronic osteomyelitis is defined as symptoms lasting more than 1 month in cases involving only avascular bone (mandible) or surrounded by new bone (capsular bone) (Brodies abscess).

The origin of bacteremia leading to chronic osteomyelitis or chronic osteomyelitis is often clinically unclear, suggesting that the most likely route of entry is via the respiratory mucosa or skin. Bacteria that cause chronic osteomyelitis are those that normally inhabit the upper respiratory tract, including *Staphylococcus aureus*, *Kingella kingae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* [4-6]. *K. kingae* has a particularly high infection rate in neonates (12%) with a decreasing infection rate in older children (6%).

Osteoarthritis (AO) can occur in any bone, but the most common site is the long tubular bone, such as the femur, tibia, or humerus [22]. In the tubular bone, the feeding artery ends in small arterial loops that empty into the sinus venosus. It has been hypothesized that bacteria can migrate from the blood vessels into the bloodstream and collect at this site (possibly due to minor trauma), leading to proliferation and suppuration. Bacterial toxins, inflammatory cytokines, ischemia, and possibly leukocytes themselves promote local bone destruction. Once suppuration occurs in the tubular bone, the infection can spread to adjacent subperiosteal areas and then to the overlying soft tissues.

Osteoarthritis (SA) may coexist with osteoarthritis, particularly in children under 2 years of age, as perforating blood vessels may be a source of infection. In addition, the joint capsule extends beyond the articular cartilage in young children, allowing for easier spread from the shinbone. The use of sensitive magnetic resonance imaging (MRI) techniques has suggested that the incidence of AO associated with SA is higher in young children, occurring in 37% of children under 2 years of age compared with only 17% of those over 10 years of age [23].

Diagnostic imaging and laboratory investigation

Pathological evaluation of a bone specimen is the gold standard for diagnosing AO, but there are also important tests that support the clinical diagnosis. Most children with a high suspicion of AO or SA will need to be seen in hospital and evaluated by an orthopedic surgeon or pediatrician to complete the testing.

The white blood cell count is often, but not always, elevated. A CRP test should be performed at presentation. CRP is an acute-phase protein produced by the liver with a short half-life of 8 hours. CRP testing is preferred over erythrocyte sedimentation rate (ESR) because it is more sensitive and decreases more rapidly with appropriate treatment. However, both ESR and CRP can be abnormal in other infectious, rheumatic, and neoplastic processes. In a study of culture-positive AO and SA, the reported sensitivity of CRP for diagnosis was 95% (95% CI 91% to 97%). ESR and CRP both peaked on day 2 of admission, with CRP levels returning to normal after 10 days. In a cohort of 265 children with confirmed musculoskeletal infection, all had elevated CRP and/or ESR within 3 days of admission [24].

Procalcitonin may be more specific in differentiating between infection and other inflammatory musculoskeletal injuries, but this test is not widely available for diagnostic purposes in Canada, nor has it been validated for the specific diagnosis of AO or SA.

Typical bone lesions of AO, when seen on plain radiographs, are localized osteolytic lesions and periosteal elevation.

However, such findings are only apparent 7 to 21 days after the onset of infection. Therefore, when symptoms first appear, the sensitivity of plain radiographs is low. Although plain radiographs often appear normal, they are necessary to exclude other important pathological lesions, such as benign or malignant tumors and fractures. However, joint effusions are often evident on plain radiographs in rheumatoid arthritis (SA). The main use of ultrasound (US) in the management of rheumatoid arthritis (AO) or ankylosing spondylitis (SA) is to detect fluid accumulation in the subperiosteal and soft tissue regions, or excess fluid in the joint space in rheumatoid arthritis (SA), especially when clinical examination is not revealing. In some cases, ultrasound can determine whether the fluid is reactive (or not). Gadolinium-enhanced MRI is the most sensitive and specific noninvasive test for the diagnosis of rheumatoid arthritis, as it provides information on soft tissue and growth plate (epiphyseal) involvement in addition to quantifying supraphysiological fluid in the joint space. MRI does not involve radiation exposure but may require general anesthesia. The earliest finding of rheumatoid arthritis on MRI is bone marrow edema. MRI is also useful in differentiating benign from malignant bone lesions from osteomyelitis [25]. MRI is not necessary when the clinical diagnosis is certain with supportive laboratory parameters and a positive clinical response to empiric therapy. Radionuclide bone scanning may be useful when radiographs are normal and MRI is not available. Even in young children, bone scanning does not require general anesthesia. The overall sensitivity of CT is estimated to be at least 80%, but the early appearance of small foci can lead to false-negative results. Bone infarctions associated with osteomyelitis can also lead to false-negative CT results. Other conditions, such as fractures or tumors, can lead to false-positive CT results. Therefore, the specificity of CT is lower than that of magnetic resonance imaging (MRI). The location of the uptake may also be important. Uptake in the metaphysis only supports the diagnosis of osteomyelitis, while uptake in other sites, such as the shaft, is more suggestive of other causes. When multiple infections are suspected, CT scanning may be a useful initial test.

CT scanning, although generally less sensitive than MRI in detecting bone marrow edema, may be useful in cases where MRI and bone scan are not possible or available, or for image-guided interventions. The optimal method for diagnosing osteomyelitis is arthrocentesis. If this is not possible, ultrasound can confirm the presence of synovial fluid, while MRI can help determine whether the synovial fluid is inflammatory. Consult a radiologist to optimize imaging.

Identifying a pathogen

Before the widespread use of the Hib conjugate vaccine, *Haemophilus influenzae* type b was a common cause of osteoarticular infections. Today*, Staphylococcus aureus* is the most common organism cultured in fully immunized individuals with OA or post-infantile rheumatoid arthritis (SA). In the United States, the increased incidence of osteoarticular infections is thought to be due to MRSA.

Blood, bone, and synovial fluid cultures are often negative (estimated to be between 30% and 90% of cases). *K. kingae* is now recognized as an important pathogen based on synovial fluid from young children. These organisms do not grow well when cultured from a cotton swab, but the yield increases significantly when the fluid is inoculated into a blood culture bottle [26]. Continued molecular testing of culture-negative specimens has also increased the diagnostic yield for *K. kingae*.

Current data support both the possibility that *K. kingae* is the predominant pathogen in children under 4 years of age with rheumatoid arthritis (with or without arthritis) and that *S. aureus* is the more common pathogen in older children.

Less common causes of AO include streptococcal species, such as *S. pneumoniae, S. pyogenes*, and *S. agalactiae*, with rare cases due to other bacteria. *Enterobacteriaceae* or fungi are uncommon causes of AO, but they occur in special populations (e.g. neonates, immunocompromised individuals, or in the setting of special environmental exposures). People with sickle cell disease are susceptible to *Salmonella* species other than *S. aureus*.

Since AO and SA are hematogenous in origin, efforts should be made to obtain adequate blood volume for culture before starting antibiotics to increase the likelihood of detecting associated transient bacteremia, particularly during the febrile phase. Higher blood volumes are more likely to yield positive blood cultures. Therefore, a total of 2 mL to 4 mL is recommended for children weighing 1 kg to 2 kg, 6 mL for children weighing 2 kg to ≤ 12 kg, 10 mL to 20 mL for children weighing 13 kg to 40 kg, and 40 mL for children > 40 kg [27]. Positive blood cultures should be repeated after 48 hours of antibiotic treatment to ensure clearance. *Staphylococcus aureus* in blood cultures should never be considered an infectious agent. In cases of rheumatoid arthritis, a joint aspiration by a radiologist or surgeon, if possible, should be attempted before antibiotics are given. This will determine whether the joint is infected, with clear therapeutic benefits. If this test is not available in the primary care setting, be sure to consult an orthopedic surgeon. In rheumatoid arthritis, surgery should also be strongly considered if subperiosteal fluid or abscess is suspected at presentation. If the patient does not improve clinically within the first few days of antibiotics, repeat imaging to identify bone or joint effusions or soft tissue abscesses and reconsider surgical debridement if any of these are detected.

Sampling for bacteriological and pathological diagnosis is important as it may reveal pathogens not treated empirically (e.g. MRSA or other bacterial or fungal pathogens).

When surgery is performed, all bone, tissue or joint fluid samples should be placed in sterile containers. The use of cotton swabs is discouraged due to low yield. Any fluid should be inoculated into blood culture bottles and tissue culture should be performed according to routine procedures. Clinical protocols should also recommend retaining a small aliquot for molecular testing in cases where the child fails to improve after empiric treatment and other pathogens are suspected.

Transition from intravenous to oral therapy and duration of treatment

Traditionally, acute osteoarticular infections in children have been treated with at least 6 weeks of antimicrobial therapy, with varying durations of intravenous therapy. Recently, studies using two large comparative databases have addressed the issue of duration of intravenous therapy more rigorously [46]. One study used a retrospective follow-up approach to compare outcomes in 1969 children older than 6 months with AO, of whom approximately half were discharged with oral antibiotics and half with intravenous antibiotics after a median hospital stay of 4 to 5 days. Initial treatment failure rates were similar in both groups (4% in the oral group and 5% in the intravenous group [OR 0.77 (95% CI 0.49 to 1.22)]) [28]. A subsequent study conducted at 38 hospitals in the United States used a retrospective observational design, matching patients by age group, length of stay, site of infection, surgical procedure, and bacterial pathogen isolation (including MRSA). This study included data from 2060 children aged 2 months to 18 years, 80% of whom had lower extremity infections. At discharge, approximately half received oral antibiotics, while the remainder received intravenous antibiotics. The median length of stay was 6 days. Excluding patients with MRSA, the most commonly prescribed antibiotics were cephalexin or cefazolin. The failure rate was 5% in the oral group and 6% in the intravenous group [29]. Complications associated with the use of intravenous catheters in outpatients significantly increased the number of emergency room visits (ranging from 4% to 41%). The cumulative and robust data suggest that oral antibiotics are usually appropriate at discharge, even for patients with bacteremia, provided negative blood cultures have been documented. Contraindications to oral therapy include poor adherence or medication monitoring, malabsorption, or delayed clinical resolution of infection. Switching to oral therapy is based on clinical improvement and a decrease in CRP. Patients with uncomplicated rheumatoid arthritis are expected to be afebrile, with significant clinical improvement after 3 to 7 days of appropriate intravenous therapy. When lower limbs are infected, weight bearing is evident; when upper limbs are infected, only mild pain with regular use is present. CRP should be markedly lower before switching to oral therapy, but the exact level to achieve is unclear: clinical course is probably a more important indicator. Other studies have used a 50% reduction in CRP over a 4-day period or a level of 20 mg/L to 30 mg/L and a good clinical response to switch to oral therapy.

A Canadian study showed that a mean dose of 40 mg/kg cephalexin orally every 8 hours resulted in pharmacokinetic parameters that were predictive of bactericidal activity in MSSA osteoarticular infections. Most clinicians recommend a dose of 120 mg/kg/day to 150 mg/kg/day orally, given three times daily (maximum 6g daily). However, some clinicians recommend lower doses: 100 mg/kg/day to 120 mg/kg/day divided into four doses, because of the short half-life of cephalexin (approximately 1 hour). Cloxacillin may also be prescribed for susceptible strains of *Staphylococcus aureus*, noting that the oral suspension has an unpleasant taste. Most clinicians recommend a dose of 100 mg/kg/day up to a maximum of 1g four times daily.

For MRSA pneumonia, the time required to meet clinical and laboratory criteria before switching to oral therapy is often longer than for other pathogens or culture-negative cases.

When local susceptibility status is known and the patient meets all clinical and laboratory criteria for oral therapy, treatment with clindamycin, trimethoprim-sulfamethoxazole, or linezolid may be considered after consultation with an infectious disease specialist.

All patients should be closely monitored. A recent review summarizing data from six studies published between 2002 and 2009 found that, although treatment durations varied, most patients with uncomplicated rheumatoid arthritis could be adequately treated with initial injection therapy followed by oral therapy for a total duration of 21 to 28 days. For most cases of uncomplicated rheumatoid arthritis that respond rapidly to empiric therapy and continue to improve with oral antibiotics, the current recommended duration of treatment is a total of 3 to 4 weeks of antibiotic therapy compared with the previously recommended 6 weeks. For rheumatoid arthritis (SA), the usual duration is 3 to 4 weeks, but most clinicians still recommend a total duration of 4 to 6 weeks if the hip is involved. These treatment duration recommendations apply regardless of whether blood cultures are positive and always assume a positive clinical response. Discontinuation of antibiotic treatment.

Classification of osteomyelitis

Histologically, osteomyelitis is classified as acute, subacute, or chronic, the presentation of each type being based on the time of onset (e.g. infection or trauma). Hematogenous osteomyelitis can be classified according to the age of the child, i.e. newborn versus infant; or according to the time of onset, i.e. acute versus subacute/chronic. Osteomyelitis is considered chronic if symptoms have been present for more than 1 month. Lauschke FHM and Frey CT have classified osteomyelitis into three groups: early acute osteomyelitis, late acute osteomyelitis, and chronic osteomyelitis. This classification system is based on clinical and radiological criteria. We have described a classification of hematogenous osteomyelitis in children into three stages: acute, intermediate, and chronic, based on clinical, radiological criteria, and time of onset.

Controversies in management

Antibiotic therapy is the gold standard for the treatment of acute osteomyelitis and septic arthritis.

Initial antibiotics are selected empirically to cover the most common pathogens causing these conditions based on the age of the child and are then adjusted based on the antibiogram obtained from cultures performed before initiating antibiotic therapy (e.g. blood cultures or, if available, intra-articular fluid or bone fragments) [30]. However, treatment of all infants and children hospitalized for these conditions is urgent due to their serious clinical conditions and risk of complications. Unfortunately, in some cases, blood cultures are negative and other invasive procedures, different from those performed in adults, are not performed in the first years of life. Therefore, it is important to know the epidemiology reported in the literature for different age groups to help select appropriate empiric therapy.

Staphylococcus aureus is undoubtedly the most common causative agent of osteomyelitis and septic arthritis in all age groups, predominantly methicillin-susceptible strains (MSSA), and is responsible for 70% - 90% of confirmed cases. As noted in adults, cases of osteoarticular infections due to methicillin-resistant *S. aureus* (MRSA) strains in pediatric patients are also increasing, and should be considered when choosing empiric antibiotic therapy [31]. In children under two months of age, *Streptococcus agalactiae* and other Gram-negative bacteria are considered potential pathogens. However, in children aged two to five years, *Streptococcus pyogenes* and *Streptococcus pneumoniae* should be considered. *Haemophilus influenzae* type b is considered a common cause of acute osteoarticular infections in children. Fortunately, following the implementation of large-scale vaccination programs, the incidence of acute osteomyelitis and septic arthritis due to *H. influenzae* type b has decreased significantly.

An emerging pathogen in the cause of acute osteoarticular infections in children is *Kingella kingae*.

This is a common commensal bacterium in the pharynx of children, particularly affecting children aged six months to four years and is difficult to isolate. The use of aerobic blood cultures or real-time polymerase chain reaction (PCR) may facilitate identification of the bacteria. Some authors have shown that *K. kingae* is the most common pathogen of acute osteoarticular infections in children under four years of age, excluding the neonatal period.

Rare causes of osteomyelitis in children include *Mycobacterium tuberculosis, Bartonella henselae*, and fungi (e.g. *Histoplasma* spp. and *Cryptococcus* spp.). These pathogens should be considered primarily in immunocompromised children.

Due to the different age distribution of the pathogens, empiric treatment in neonates should include oxacillin combined with gentamicin. In children over three months of age, for MSSA, *S. pyogenes*, and *K. kingae*, antistaphylococcal penicillins such as nafcillin or oxacillin or first-generation cephalosporins such as cefazolin should be used. However, in cases where MRSA infection is highly suspected (e.g. countries with a MRSA prevalence of ¥10%, patients with a history of intensive care unit hospitalization, immunocompromised patients), antibiotics effective against this pathogen should be recommended. In these cases, the first choice may be to use clindamycin, an antibiotic of the lincosamide group, the efficacy of which has been demonstrated [32]. If the local resistance rate to clindamycin is greater than 10%, the first choice is vancomycin. However, this glycopeptide has the disadvantage of requiring intravenous administration and therapeutic drug monitoring to detect possible toxic effects. In cases where MRSA does not respond to clindamycin and vancomycin, an alternative is linezolid.

Linezolid belongs to the oxazolidinones group and is effective against infections caused by Gram-positive bacteria, such as MRSA, coagulase-negative staphylococci, glycopeptide-resistant enterococci, and penicillin-resistant pneumococci. Linezolid also has the advantage of being very well absorbed even when administered orally. In addition, many studies have established the necessary dosage for neonatal and pediatric patients; However, it is expensive and, with prolonged treatment, may be associated with the development of hematological abnormalities as well as optic and peripheral neuropathy.

Even daptomycin, a lipopeptide antibiotic, may be considered a useful antibiotic in the case of multidrug-resistant Gram-positive bacteria. However, further studies in neonates and pediatric patients are needed to confirm its use in children.

Trimethoprim-sulfamethoxazole has been used successfully to treat MRSA skin and soft tissue infections. A small retrospective study by Messina., *et al.* showed that in cases of MRSA osteomyelitis in children, trimethoprim-sulfamethoxazole was an effective treatment option. However, larger clinical trials are needed to confirm this treatment option [33]. In recent years, acute bone and joint infections caused by Panton-Valentine leukocidin-producing strains of *S. aureus* have been reported, although not frequently in Europe. Panton-Valentine leukocidin (PVL) is a toxin that causes tissue necrosis and neutrophil destruction, thus facilitating the spread of infection, and children affected by this pathogen have a more aggressive clinical presentation. The risk of complications such as subperiosteal abscesses, pyomyositis, necrotizing fasciitis and orthopedic sequelae is high. Therefore, bone or joint infections caused by PVL-producing strains of *S. aureus* require more aggressive and prolonged antibiotic treatment, often requiring multiple surgical debridements. Flucloxacillin, clindamycin or linezolid are recommended in these cases, with daptomycin considered a second-line antibiotic. Daptomycin was used successfully in a recent case report of a child with PVL-positive staphylococcal osteomyelitis.

Salmonella spp. are common causes of acute osteoarticular infections in developing countries and in patients with sickle cell disease [34]. For this type of infection, third-generation cephalosporins such as cefotaxime, ceftriaxone, or a fluoroquinolone should be considered.

Finally, *Candida* spp. are another pathogen that can be identified from some cases of acute osteomyelitis (mainly ankylosing spondylitis) that require prolonged antifungal therapy and surgical debridement.

However, identification of the pathogen causing acute osteoarticular infections is time-consuming because some pathogens are slow-growing. Furthermore, invasive procedures requiring anesthesia are limited in pediatric patients for ethical reasons. According to several studies, this appears to be possible in 30% to 70% of cases, and the severity of the clinical picture and the age of the patient are important factors in choosing antibiotic therapy.

Other drugs

In the case of septic arthritis, two clinical trials have investigated the effect of dexamethasone on antibiotic therapy. In both of these double-blind, placebo-controlled studies, four days of intravenous dexamethasone in combination with antibiotic therapy was observed to result in a shorter duration of symptoms and mild residual joint dysfunction at the end of antibiotic therapy and at follow-up. These results were recently confirmed in a large retrospective study by Fogel., *et al*. [35], who analyzed 116 pediatric patients with septic arthritis, 90 of whom were treated with antibiotics alone and 26 of whom were treated with antibiotics in combination with intravenous dexamethasone for several days. The latter group had a shorter duration of fever (mean 2.3 days vs 3.9 days, $p = 0.002$), faster clinical improvement (mean 6.3 days vs 10.0 days, no pain/limitation, $p < 0.001$), faster reduction of CRP levels to <1 mg/dL (mean 5.3 days vs 8.4 days, $p = 0.002$), shorter duration of parenteral antibiotic treatment (mean 7.1 days vs 11.4 days, $p < 0.001$), and shorter hospital stay (mean 8 days vs 10.7 days, $p = 0.004$).

However, although these studies suggest that corticosteroid treatment is associated with better outcomes, more research is needed to confirm these results. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used for pain relief.

Furthermore, in adult patients with orthopedic implants, biofilms have been shown to cause antibiotic treatment failure. *In vitro* findings suggest that local antibiotic delivery may be an effective strategy for the prevention and/or treatment of open fractures where biofilms may develop [36].

Duration of antibiotic treatment

Acute osteomyelitis and septic arthritis require prompt antibiotic treatment, starting with intravenous antibiotics and then switching to oral antibiotics to avoid complications. However, there is no consensus on the duration of antibiotic treatment and when to switch to oral therapy.

Traditionally, children with acute osteomyelitis and septic arthritis are treated with intravenous antibiotics for several weeks, then switched to oral therapy when the wound is nearly healed [37].

However, the prolonged duration of parenteral therapy is associated with prolonged hospital stays, high costs, and sometimes the need for central venous access. Some centers initiate peripheral intravenous therapy for a few days during the hospital stay and then place a central venous catheter to provide parenteral therapy at home for four to six weeks [38].

Some authors have suggested the possibility of reducing the duration of intravenous antibiotic therapy to only a few days and then continuing oral therapy. In a prospective randomized study by Peltola., *et al.* pediatric patients with acute osteomyelitis predominantly caused by MSSA strains who received 20 days of oral antibiotics (clindamycin or a first-generation cephalosporin) achieved similar outcomes as patients treated for 30 days after initial intravenous therapy of two to four days in both groups. Jagodzinski., *et al.* also obtained similar results in 70 children aged two weeks to 14 years with acute osteomyelitis or septic arthritis who were treated for three to five days with high-dose intravenous therapy followed by three weeks of oral therapy [39]. However, in the case of MRSA or PVL *S. aureus*, four to six weeks of treatment is recommended. In addition, studies have demonstrated that two to three weeks of high-dose, well-absorbed antibiotics, initiated intravenously and requiring only a single joint aspiration, appear to be sufficient for the treatment of septic arthritis in children [40]. Oral antibiotics reduce the risk of complications associated with prolonged parenteral antibiotics at home and reduce the number of emergency department visits and readmission rates.

Certainly, the child should not have serious complications, be able to receive oral antibiotic therapy, and tolerate the medication; The antibiotic must also have high oral bioavailability and reach adequate concentrations at the site of infection. Finally, the oral antibiotic must have the same level of antibacterial coverage as the parenteral antibiotic. The transition from intravenous to oral antibiotic therapy may also be guided by other factors. Specifically, there should be an improvement in the child's general condition, a stable fever reduction, and a significant decrease in C-reactive protein (CRP). Recently, Chou., *et al.* found that a 50% decrease in CRP associated with clinical improvement in the patient can be used to initiate a switch to oral antibiotic therapy in acute bacterial bone and joint infections. Similar results were obtained in a retrospective study by Pääkkönen., *et al.* in which patients immunocompromised infants or children, as well as cases due to *Salmonella* spp. or MRSA, require longer treatment. Interestingly, Jagodzinski., *et al.* demonstrated that initial CRP levels greater than 10 mg/dL and temperatures greater than 38.4°C should be considered predictors of the need for prolonged intravenous antibiotics [39]. In cases of persistently elevated CRP values despite antibiotic treatment, complications should be suspected and antibiotic therapy should be adjusted or prolonged.

In conclusion, a short course of intravenous antibiotics followed by oral antibacterial therapy for two to three weeks for septic arthritis and three weeks for osteomyelitis appears to be safe and effective in uncomplicated osteoarticular infections. In other cases, intravenous therapy should be extended for at least three weeks for septic arthritis and four to six weeks for osteomyelitis.

However, the duration of anti-infective therapy should always be based on clinical judgment, objective diagnostic data, and the oral bioavailability of the different antibiotics.

Surgery

Along with antibiotics, surgery plays a key role in the treatment of acute osteomyelitis and septic arthritis in children [42].

First, surgery allows for obtaining useful biological samples to identify the causative agent and then guide the selection of appropriate antibiotics for treatment. Furthermore, in cases involving joints, surgical joint drainage reduces the risk of complications such as avascular necrosis of bone and permanent cartilage damage due to increased intra-articular pressure, resulting in better outcomes [43]. Furthermore, arthroscopic joint lavage has been shown to be safe and effective in the treatment of septic arthritis in very young children [44]. In addition, surgery alters the course of osteonecrosis, reduces vascularity and thus reduces antibiotic penetration at the site of infection, removes demineralized bone, and cleans the surrounding soft tissue, thereby reducing the bacterial load.

However, in cases of uncomplicated acute osteoarticular infections, surgery may not be necessary. Antibiotic treatment should be considered in patients who do not respond to antibiotic treatment because of suspected underlying complications. Acute bone and joint infections caused by MRSA or PVL-producing *Staphylococcus aureus* often require more surgical procedures because these organisms have a more severe clinical course.

Debridement

Osteotomy followed by drainage of any associated soft tissue abscess remains the mainstay of treatment, although there are no clear recommendations as to when excision is necessary. Osteotomy is often indicated as part of initial treatment when there is an underlying orthopedic device and necrotic bone. Bone stabilization is an essential component of osteotomy and may reduce healing time and complications.

Osteotomy followed by antibiotic therapy shortens hospital stay, reduces medical costs, effectively controls infection, and prevents complications from prolonged systemic antibiotic use. Osteotomy may be supplemented by placement of an antibiotic-loaded collagen sponge, which has some evidence to support improved outcomes. Hyperbaric oxygen therapy can be used as an adjunct and may be particularly useful in cases of chronic osteomyelitis.

Special considerations

When selecting a treatment strategy for osteomyelitis, certain patient groups require special consideration, such as children and patients with prosthetic joints, vertebral osteomyelitis, and diabetes. The treatment of these groups is beyond the scope of this article. This article updates an earlier article on this topic by Hatzenbuehler., *et al*. [45] Data Source: A PubMed search was completed in Clinical Queries using the key terms osteomyelitis, diagnostic imaging, and treatment. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews.

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e database, the Database of Abstracts of Reviews of Effectiveness (DARE).

Limitation of the Study

1. This was a retrospective study;
2. There was no control group for each bone location; and
3. Treatment did not differentiate between long and flat bones nor compare these two bone types separately.

Conclusion

Acute osteomyelitis is an infection with increasing frequency in children. Acute osteomyelitis requires careful evaluation, diagnosis and treatment to avoid serious sequelae.

Currently, the accepted initial treatment of acute osteomyelitis includes empiric antibiotic therapy, which can cover the potential pathogens based on the age group. However, there is still no consensus on which antibiotics should be used in different countries.

In recent years, the emergence of particularly virulent and antibiotic-resistant bacterial strains has been observed. These pathogens are associated with very aggressive and dangerous clinical symptoms. Therefore, in these cases, as well as in neonates and patients with underlying chronic diseases, it is extremely important to obtain as many reliable specimens as possible for microbiological testing and to initiate prompt, aggressive and prolonged intravenous treatment.

However, there are still some shortcomings in the management of acute osteoarticular infections.

In addition, data on the efficacy and safety of corticosteroids in patients with acute osteoarticular infections are limited, and further research on this issue would be useful. Furthermore, the role of biofilms in treatment failure in pediatric patients needs to be evaluated. Finally, the emergence of antibiotic-resistant bacterial strains has made it urgent to focus research on finding new molecules with good bone and joint penetration to overcome this problem.

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