Osteomyelitis: Pathophysiology, Clinical Manifestations, Diagnostic Evaluation, Microbiological Characteristics, Contemporary Therapeutic Strategies, and Recent Advances in the Prevention and Management of Bone Infection-An Updated Review

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Abstract

Background: Osteomyelitis is a complex and potentially disabling infectious disease of bone and bone marrow that remains a significant clinical challenge despite advances in diagnostic and therapeutic strategies. Progressive bone inflammation, microbial persistence, and extensive tissue destruction contribute to considerable morbidity, impaired function, and reduced quality of life when diagnosis or treatment is delayed. The predominance of *Staphylococcus aureus* and its sophisticated virulence mechanisms, including biofilm formation, intracellular persistence, phenotype switching, and invasion of the osteocyte lacuno-canalicular network, further complicate disease management and increase the risk of chronic infection.

Aim: This review aimed to comprehensively summarize the current evidence regarding the pathophysiology, microbiology, clinical manifestations, diagnostic approaches, therapeutic strategies, and emerging advances in the prevention and management of osteomyelitis.

Methods: A comprehensive narrative review of the contemporary literature was conducted to evaluate current evidence on the mechanisms of disease, causative microorganisms, clinical presentation, diagnostic modalities, antimicrobial therapy, surgical management, biomaterial-based interventions, and novel therapeutic approaches for osteomyelitis.

Results: Current evidence demonstrates that *Staphylococcus aureus* remains the principal pathogen responsible for osteomyelitis through multiple virulence mechanisms that promote chronicity and antimicrobial resistance. Magnetic resonance imaging is the most sensitive imaging modality for early diagnosis, whereas bone biopsy with microbiological culture and histopathological examination remains the diagnostic gold standard. Management requires a multidisciplinary approach integrating accurate microbiological diagnosis, targeted antimicrobial therapy, and appropriate surgical debridement when indicated. Recent evidence supports shorter intravenous antibiotic courses followed by oral therapy in selected uncomplicated cases, whereas chronic osteomyelitis requires prolonged pathogen-directed antimicrobial treatment combined with extensive surgical intervention.

Conclusion: Successful management of osteomyelitis requires early diagnosis, individualized multidisciplinary treatment, and integration of medical and surgical interventions. Emerging biomaterial technologies and targeted antimicrobial strategies offer considerable potential to improve treatment outcomes, reduce recurrence, and enhance bone healing. Continued research is essential to optimize treatment duration, develop therapies targeting persistent intracellular pathogens, and establish evidence-based protocols for incorporating regenerative biomaterials into routine clinical practice.

Keywords: Osteomyelitis; Bone infection; *Staphylococcus aureus*; Biofilm; Magnetic resonance imaging; Bone biopsy; Antimicrobial therapy; Surgical debridement; Biomaterials; Bone regeneration.

Introduction

Osteomyelitis is an inflammatory condition of bone and bone marrow triggered by infectious pathogens, most commonly bacteria, which may induce progressive bone destruction and, if inadequately treated, result in chronic pain, deformity, pathological fracture, and substantial impairment of quality of life [1][10]. The term encompasses a heterogeneous group of infections that vary considerably in their etiology, pathogenesis, clinical presentation, and optimal management strategies [2][5]. Despite significant advances in diagnostic imaging, antimicrobial therapy, and surgical techniques over recent decades, osteomyelitis remains a formidable clinical challenge, characterized by high rates of recurrence, substantial healthcare costs, and significant patient morbidity [1][11]. The global burden of osteomyelitis is considerable and appears to be increasing, driven in part by the rising prevalence of diabetes mellitus, peripheral vascular disease, and an aging population, alongside the emergence of multidrug-resistant organisms that complicate treatment [2][12]. Acute hematogenous osteomyelitis predominantly affects children, with an increasing incidence observed in recent years, while chronic osteomyelitis more commonly afflicts adults, frequently in the setting of open fractures, previous orthopedic surgery, or contiguous spread from infected soft tissues [2][5][13]. The management of osteomyelitis demands a multidisciplinary approach integrating the expertise of infectious disease specialists, orthopedic surgeons, radiologists, and microbiologists to achieve optimal outcomes [6][14]. This updated review aims to provide a comprehensive synthesis of current knowledge regarding the pathophysiology, clinical manifestations, diagnostic evaluation, microbiological characteristics, contemporary therapeutic strategies, and recent advances in the prevention and management of osteomyelitis. By integrating findings from recent guidelines, clinical studies, and translational research, this review offers practical, evidence-based guidance for clinicians while identifying priority areas for future investigation.

Pathophysiology of Osteomyelitis

The pathophysiology of osteomyelitis is a complex, dynamic process involving the interplay between invading microorganisms, host immune responses, and the unique anatomical and physiological characteristics of bone tissue [1][9]. Bone infection can arise through three principal routes: hematogenous spread of organisms from a distant source of infection, contiguous spread from adjacent infected soft tissues or prosthetic joints, and direct inoculation through open fractures or surgical procedures [5][15]. Hematogenous osteomyelitis, which accounts for the majority of cases in children, typically affects the metaphyses of long bones where the slow, turbulent blood flow in the sinusoidal venous system facilitates bacterial seeding and subsequent proliferation [2][13]. Contiguous spread, responsible for approximately 80% of osteomyelitis cases overall, commonly involves the feet in patients with diabetes or peripheral vascular disease and is frequently polymicrobial in nature [5][15]. Once bacteria establish a foothold in bone tissue, a cascade of inflammatory events is initiated that ultimately leads to progressive bone destruction [1][9]. The inflammatory response triggers the release of proteolytic enzymes and pro-inflammatory cytokines from activated neutrophils and macrophages, which degrade bone matrix and stimulate osteoclastic bone resorption [3][9]. Concurrently, bacterial proliferation within the bone microenvironment leads to the formation of microabscesses, which may coalesce to form larger intramedullary abscesses [1][10]. The resulting increase in intramedullary pressure compromises local blood supply, leading to ischemic necrosis of bone tissue and the formation of sequestra—devitalized fragments of bone that serve as nidi for persistent infection [2][5]. The host response attempts to wall off the infection through the formation of new bone around the necrotic focus, creating an involucrum that may contain draining sinuses in chronic cases [5][10].

The majority of osteomyelitis cases, particularly chronic infections, are caused by *Staphylococcus aureus*, the most prevalent and devastating pathogen in bone infection, partially due to its sophisticated resistance mechanisms against both the immune system and antibiotic therapies [1][3]. The accumulated discoveries of recent years have identified multiple distinct strategies associated with chronicity and recurrence that collectively explain the remarkable persistence of *S. aureus* in bone tissue [1][10]. These include biofilm development, the formation of small colony variants (SCVs), the establishment of staphylococcus abscess communities (SACs), invasion of the osteocyte lacuno-canalicular network (OLCN) of cortical bones, and the activity of *S. aureus* protein A (SpA) [1][3]. Biofilm formation represents perhaps the most critical virulence mechanism in chronic osteomyelitis [1][10]. Within biofilms, bacteria exist in a sessile, metabolically dormant state embedded within a self-produced extracellular polymeric matrix that provides protection against both host immune defenses and antimicrobial agents [1][11]. The biofilm environment promotes the development of small colony variants, phenotypic variants characterized by slow growth and enhanced intracellular survival capacity, which are notoriously difficult to eradicate with conventional antibiotic therapy [1][3]. Furthermore, *S. aureus* has demonstrated the remarkable ability to invade and survive within osteoblasts and osteocytes, the cells responsible for bone formation and maintenance, establishing intracellular reservoirs that contribute to disease chronicity and recurrence following apparently successful treatment [3][9]. Infected osteoblasts and osteocytes not only serve as reservoirs in chronic cases but also play an active role in the osteoimmunology process, notably by producing mediators that promote the bone resorption activity of osteoclasts, thereby disrupting bone homeostasis and perpetuating the cycle of bone destruction [3][9]. The invasion of the osteocyte lacuno-canalicular network of cortical bones represents a recently elucidated mechanism by which *S. aureus* establishes deep, inaccessible foci of infection that are particularly resistant to both host defenses and therapeutic intervention [1][3].

Classification and Clinical Manifestations

Osteomyelitis can be classified by duration, pathogenesis, location, extent, and host status, with two principal classification systems currently in clinical use: the Waldvogel classification and the Cierny-Mader classification [2][6]. The Waldvogel classification is an etiologic system that categorizes osteomyelitis according to the route of infection (hematogenous versus contiguous spread) and the duration of infection (acute versus chronic) [6][14]. The Cierny-Mader classification, by contrast, is a descriptive anatomico-physiological staging system that categorizes osteomyelitis based on the anatomy of the bone infection and the physiology of the host, allowing stratification of long bone osteomyelitis and the development of comprehensive treatment guidelines for each stage [2][6][14]. Because the Waldvogel classification addresses etiology while the Cierny-Mader classification provides anatomical and physiological staging, both classifications can be simultaneously used to provide a comprehensive characterization of the infection [6][14]. The Cierny-Mader staging system considers four anatomical types—medullary, superficial, localized, and diffuse—and three host categories—A (normal host), B (systemic or local compromise), and C (treatment worse than disease)—to guide treatment decisions and predict outcomes [2][6][14].

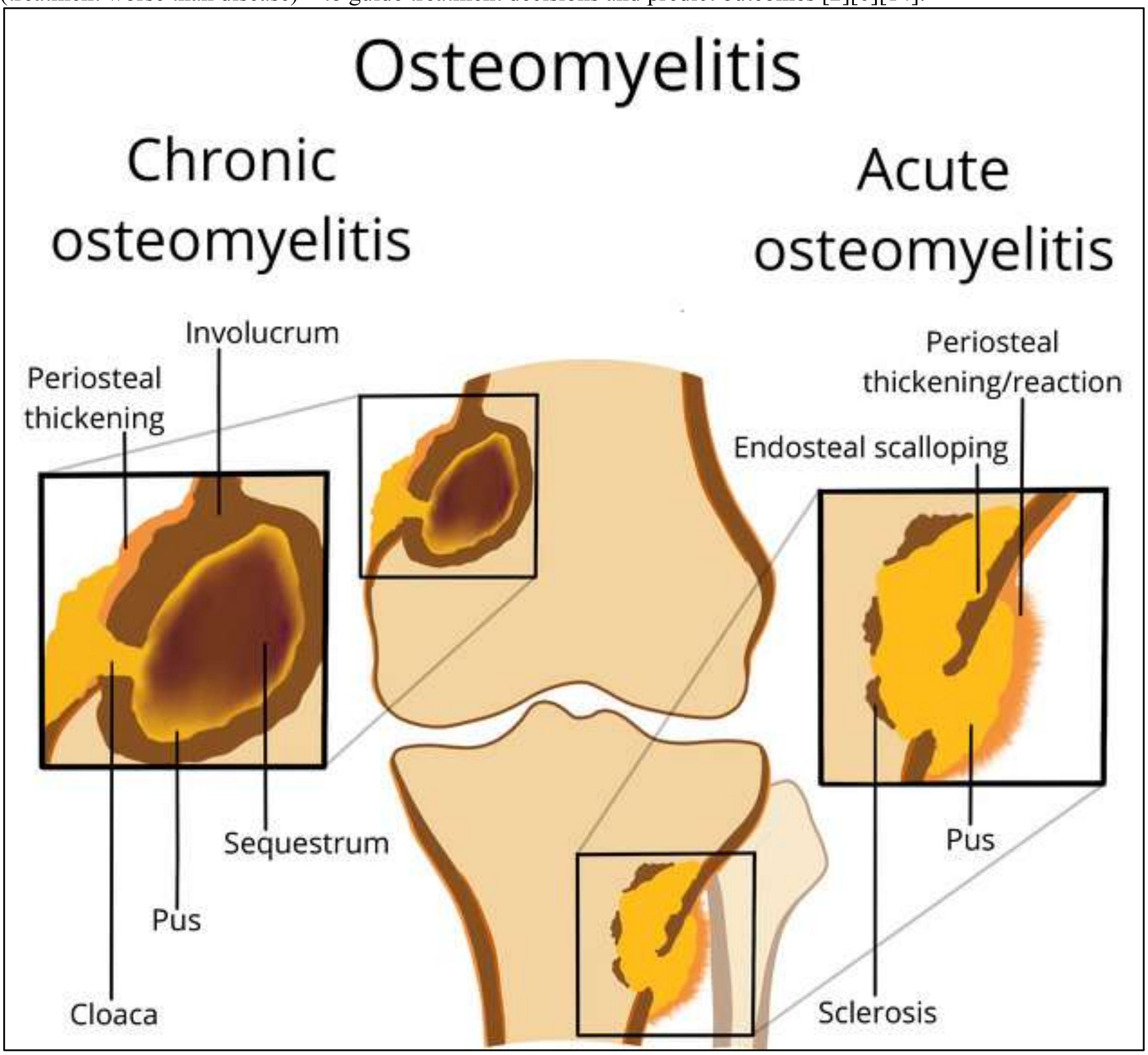

Fig. 1: Classification of Osteomyelitis.

Acute osteomyelitis typically presents with the sudden onset of localized bone pain, tenderness, warmth, and swelling, accompanied by constitutional symptoms including fever, malaise, and fatigue [2][5][13]. In children with acute hematogenous osteomyelitis, the infection most commonly involves the metaphyses of long bones, particularly the distal femur, proximal tibia, and proximal humerus, and may present with refusal to bear weight or a limp [2][13]. The clinical presentation in neonates and young infants may be more subtle, with pseudoparalysis of the affected limb, irritability, and poor feeding being prominent features [5][13]. Laboratory findings in acute osteomyelitis typically reveal elevated inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as leukocytosis, though normal values do not exclude the diagnosis [2][5]. Blood cultures are positive in approximately 50-70% of cases of acute hematogenous osteomyelitis and should be obtained before the initiation of antibiotic therapy whenever possible [5][11].

Chronic osteomyelitis is defined by the persistence of infection for more than six weeks and is characterized by the presence of necrotic bone (sequestrum), new bone formation (involucrum), and often a discharging sinus tract [2][5][10]. Unlike acute osteomyelitis, chronic infection may present with localized bone pain and tenderness without constitutional symptoms, though acute exacerbations can occur [5][15]. The clinical hallmark of chronic osteomyelitis is the presence of a chronic draining sinus, which may intermittently discharge purulent material [2][10]. Chronic osteomyelitis most commonly occurs in adults with a history of open fracture, previous orthopedic surgery, or a discharging sinus, and in patients with diabetes, peripheral vascular disease, or other immunocompromising conditions [2][5][11]. The Cierny-Mader staging system is particularly valuable in chronic osteomyelitis, as it guides the selection of appropriate surgical and medical interventions based on the anatomical extent of disease and the physiological status of the host [6][14].

Vertebral osteomyelitis, a form of hematogenous osteomyelitis affecting the spinal vertebrae, presents with insidious onset back pain and systemic symptoms, and its diagnosis is frequently delayed due to the low specificity of clinical manifestations [5][16]. This condition is most commonly caused by *Staphylococcus aureus* or gram-negative bacilli and requires prompt diagnosis and treatment to prevent severe neurological sequelae [16][17]. Diabetic foot osteomyelitis represents a particularly challenging form of contiguous osteomyelitis, occurring in the setting of diabetes-related foot infections and constituting a leading cause of non-traumatic lower extremity amputation [8][18]. The management of diabetic foot osteomyelitis mandates a comprehensive strategy that addresses both the infectious and vascular aspects of the condition, often requiring a collaborative approach involving multiple specialties [18][19].

Diagnostic Evaluation

The diagnostic evaluation of suspected osteomyelitis begins with a thorough clinical assessment, including a detailed history and physical examination to identify risk factors, localizing signs, and systemic manifestations of infection [2][5]. Suggestive clinical features include fever, bone pain, reduced mobility, local erythema, tenderness, warmth, and swelling, as well as reduced range of movement in adjacent joints [5][11]. Initial laboratory investigations should include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, and blood cultures [2][5]. Elevated inflammatory markers support the diagnosis and provide baseline values for monitoring treatment response, though normal values do not exclude osteomyelitis, particularly in chronic cases or immunocompromised patients [2][11]. Blood cultures should be obtained before the initiation of empirical antibiotic therapy whenever clinically feasible, as positive results may obviate the need for invasive bone biopsy [5][14].

Imaging plays a pivotal role in the early detection and assessment of osteomyelitis, guiding both medical and surgical interventions [4][5]. Plain radiography is the initial imaging modality of choice and should be obtained to screen for acute and chronic osteomyelitis; however, it often fails to detect early osteomyelitis, as radiographic changes typically do not appear until 10-14 days after the onset of infection, when bone demineralization has reached 30-50% [4][5]. Magnetic resonance imaging (MRI) is the imaging modality with the greatest sensitivity for diagnosing osteomyelitis and is particularly valuable for early detection, as it can identify bone marrow edema and soft tissue involvement before radiographic changes become apparent [4][5][11]. MRI is now the preferred imaging method for diagnosing osteomyelitis due to its exceptional soft tissue contrast and ability to delineate the full extent of bone and soft tissue infection [4][11]. Computed tomography (CT) is valuable for assessing bony destruction and chronic changes, particularly in identifying sequestra and evaluating cortical bone involvement, while ultrasonography is beneficial in pediatric cases and for guiding diagnostic and therapeutic interventions [4][5]. Nuclear medicine techniques, including bone scintigraphy, gallium scanning, and 18F-FDG PET-CT, offer high sensitivity and specificity, especially in complex or multifocal cases where MRI may be contraindicated or equivocal [4][14]. The combination of these imaging modalities, tailored to the clinical context, enhances diagnostic accuracy and guides effective treatment strategies [4][5].

The diagnosis of osteomyelitis should be confirmed by culture obtained from biopsy of the involved bone, as surface swabs or sinus tract cultures have limited value and correlate poorly with bone biopsy cultures except in cases of methicillin-resistant *Staphylococcus aureus* (MRSA) infection [2][5][11]. Bone biopsy samples isolating bacteria with histological findings of osteonecrosis and inflammatory disease represent the reference standard for the diagnosis of osteomyelitis [5][11]. Image-guided biopsies in patients with suspected native vertebral osteomyelitis are recommended to establish the microbiological diagnosis and guide antibiotic therapy [14][16]. For osteomyelitis from contiguous spread of infection, wound culture is poorly correlated with bone biopsy culture for all organisms except MRSA; unless MRSA is grown, surgical bone biopsy is recommended to define the correct pathogen [14][15]. In addition to conventional culture techniques, molecular diagnostic methods including polymerase chain reaction (PCR) and MALDI-TOF mass spectrometry may be employed to identify organisms that are fastidious, slow-growing, or have been rendered non-viable by prior antibiotic exposure [5][11]. Histopathological examination of bone biopsy specimens is essential to confirm the diagnosis, as it can demonstrate the presence of acute or chronic inflammation, osteonecrosis, and the characteristic features of osteomyelitis even when cultures remain negative [2][5].

Staphylococcus aureus is the most common etiological agent in all forms of osteomyelitis, accounting for the majority of cases, particularly in acute hematogenous osteomyelitis and chronic infections [1][5][15]. Methicillin-

resistant *Staphylococcus aureus* (MRSA) has emerged as a pathogen of increasing concern, with rates having risen dramatically over the past decade, and MRSA infection is associated with more severe disease, higher rates of treatment failure, and prolonged antibiotic requirements [1][12][15]. In cases of contiguous spread from adjacent infected tissue or open wounds, which account for approximately 80% of osteomyelitis, the infection is often polymicrobial, with *Staphylococcus aureus* (including both methicillin-sensitive and methicillin-resistant strains) present in ≥50% of patients, alongside streptococci, gram-negative enteric organisms, and anaerobic bacteria [5][15]. A microbiological evaluation from a tertiary care hospital found that the most common causative organism was *Staphylococcus aureus* (46.9%), with methicillin resistance observed in 41.9% of isolates; among Gram-negative isolates, the Enterobacterales group predominated (22.7%) [12]. Other pathogens that may cause osteomyelitis include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* species, *Salmonella* species (particularly in patients with sickle cell disease), and, in immunocompromised patients, fungi and mycobacteria [2][5][15].
Antimicrobial resistance represents a significant and growing challenge in the management of osteomyelitis, complicating treatment selection and increasing the risk of treatment failure [1][12][15]. MRSA, in particular, poses substantial therapeutic difficulties, as standard beta-lactam antibiotics are ineffective, and treatment requires the use of agents such as vancomycin, daptomycin, or linezolid [14][15]. Data suggest that MRSA organisms with a vancomycin minimum inhibitory concentration (MIC) of 2 µg/mL or greater have a higher rate of treatment failure with vancomycin therapy, and in this situation, an alternative agent such as daptomycin should be used [14][15]. The emergence of multidrug-resistant Gram-negative organisms further complicates treatment, particularly in healthcare-associated infections and in patients with prior antibiotic exposure [12][15]. Antimicrobial resistance is a significant global problem, including in low- and middle-income countries, and extensively drug-resistant bacteria have been identified in the context of musculoskeletal infections during armed conflicts [7][8].

Contemporary Therapeutic Strategies

The treatment of osteomyelitis requires an integrated approach involving both surgical and pharmacological interventions, with the specific strategy determined by the duration and severity of infection, the causative pathogen and its antimicrobial susceptibility profile, the anatomical location and extent of bone involvement, and the physiological status of the host [2][6][14]. Current trends in long bone osteomyelitis therapy emphasize early diagnosis and aggressive treatment [6]. Surgical treatment involves debridement of necrotic bone and tissue, obtaining appropriate cultures, managing dead space, and, when necessary, obtaining bone stability [6][10]. Medical therapy includes improving any host deficiencies, initial antibiotic selection based on the most likely pathogens and local epidemiology, and antibiotic modification based on culture and susceptibility results [2][6][14]. Ideally, the choice of an antimicrobial regimen for treatment of osteomyelitis is determined on the basis of culture and sensitivity testing of the specimen obtained from the infective site or the blood [14][15].
Antibiotic therapy for hematogenous osteomyelitis should be pathogen-directed, based on the results of cultures from bone biopsy and/or blood cultures [2][14][15]. For uncomplicated cases of osteomyelitis, the duration of antimicrobial therapy is typically 3 to 4 weeks, while for MRSA, a minimum of 6 weeks of antibiotic therapy is recommended [2][6][14]. Parenteral therapy or administration of antibiotics with high oral bioavailability is preferred, and several recent studies indicate that a short course of intravenous treatment followed by oral therapy is as effective as the traditional prolonged intravenous treatment, with a lower incidence of complications [2][6][13]. The Infectious Diseases Society of America (IDSA) and Pediatric Infectious Diseases Society (PIDS) have published clinical practice guidelines providing evidence-based recommendations for the diagnosis and treatment of acute hematogenous osteomyelitis in children [2][13][20]. For chronic osteomyelitis, surgery to remove necrotic bone is the primary treatment, as antibiotics alone cannot achieve a cure [5][10]. Chronic osteomyelitis with multiple recurrences of disease in the same location with the same organism, usually *S. aureus*, may require extensive debridement followed by a prolonged (up to 8 weeks) intravenous antibiotic course for cure; however, failing this, lifelong suppression may be needed [14][15].
Surgical intervention is a cornerstone of osteomyelitis management, particularly in chronic cases, and involves radical debridement of all necrotic and infected tissue, drainage of abscesses, management of dead space, and, when indicated, stabilization of the bone [2][6][10]. The primary goal of surgical debridement is to remove all devitalized tissue, including sequestra, and to eliminate the nidus of infection, thereby creating an environment conducive to healing and antibiotic penetration [2][10]. Following debridement, the management of dead space is critical to prevent re-infection and facilitate bone healing; this may be achieved through the use of antibiotic-loaded polymethylmethacrylate (PMMA) cement beads or spacers, which provide high local concentrations of antibiotics while maintaining structural support [2][6][25]. Antibiotic-loaded bone cement is a widely utilized systemic approach in the treatment of osteomyelitis with an infected bone defect, with the premise that high-dose local delivery is crucial for eradicating biofilm-associated bacteria [25][26]. In cases of extensive bone loss, reconstructive procedures including bone grafting, vascularized bone flaps, and the Ilizarov technique may be required to restore bony integrity and function [2][10]. A meta-analysis revealed no significant difference in cure rates between single and two-stage surgical treatments for chronic osteomyelitis in long bones, supporting the efficacy of both approaches [2][10]. Surgery combined with anti-infective chemotherapy leads to long-lasting containment of infection in 70% to 90% of cases [2].

Recent advances in biomaterials and drug delivery systems have opened new avenues for the treatment of osteomyelitis [7][8][17]. Bioactive glass has shown promise as a bone void filler with dual-action properties, combining bacteriostatic and bactericidal activity with bone regenerative potential [7][8][20]. Bioactive glass binds to bone, stimulates bone formation, causes no harmful immune response, and has antimicrobial properties [7][20]. A systematic review on bioactive glass as a treatment for limb osteomyelitis and infected nonunion demonstrated the potential of this biomaterial, with studies supporting bioactive glass use with high rates of bone healing and infection resolution, and comparative studies finding non-inferiority with established treatments such as antibiotic-containing calcium sulphate and polymethylmethacrylate cement spacers [7][20]. Bioactive glass S53P4 has been shown to be a safe and effective adjunct in osteomyelitis management, demonstrating high long-term infection control, robust bone regeneration, and a low complication profile [8][20]. Antibiotic-eluting scaffolds capable of eliminating infection and facilitating bone healing represent another promising one-stage therapy for osteomyelitis [7][19]. Novel antibiotic-eluting depot technology has demonstrated efficacy in eradicating *S. aureus* in implant-associated osteomyelitis in animal models without the need for systemic antibiotics [19][25]. These emerging approaches hold particular promise for the management of challenging cases, including those involving multidrug-resistant organisms and large bone defects [7][8][17].

Recent Advances in Prevention and Management

Recent research has substantially advanced our understanding of the pathogenesis of osteomyelitis, particularly the mechanisms by which *Staphylococcus aureus* establishes persistent, treatment-resistant infection [1][3][9]. The recognition that *S. aureus* can survive intracellularly within osteoblasts and osteocytes, as well as within macrophages, has profound implications for treatment, as conventional antibiotics may not achieve adequate intracellular concentrations to eradicate these persistent reservoirs [3][9][21]. Infected osteoblasts and osteocytes not only serve as reservoirs but also play an active role in the osteoimmunology process by producing mediators that promote bone resorption, thereby disrupting bone homeostasis [3][9]. The intracellular survival of *S. aureus* in macrophages during osteomyelitis represents another mechanism by which the pathogen establishes chronic bone infection, and emerging insights into how *S. aureus* manipulates macrophage function have highlighted therapeutic opportunities targeting macrophage polarization to improve immune-mediated clearance and bone repair [21]. These findings have opened new avenues for therapeutic intervention, including strategies aimed at enhancing intracellular killing of bacteria, modulating the host immune response, and targeting the osteoimmunological pathways that drive bone destruction [3][9][21].

The development of advanced biomaterials and local drug delivery systems represents one of the most exciting frontiers in osteomyelitis management [7][8][17][20]. Antibiotic-loaded bone cement, while a mainstay of treatment, has limitations including low efficiency against bacteria in biofilms, and novel biomaterials are being developed to address these shortcomings [25][26]. Borosilicate bioactive glass has been shown to eliminate bacterial infection through biofilm inhibition, oxidative stress, and ATP disruption, offering a promising alternative to conventional antibiotic-loaded PMMA cement [25]. Antibiotic-eluting scaffolds with responsive dual-release kinetics have been engineered to eliminate infection while facilitating bone healing, and studies have shown that these scaffolds, when implanted into infected bone defects, can achieve one-stage treatment of osteomyelitis [19][25]. Drug-free approaches, such as triboelectric immunotherapy, have also been explored as strategies for osteomyelitis treatment and recurrence prevention, offering the potential for efficient, long-acting, and multifunctional treatment without the risk of antibiotic resistance [19].

Significant advances have been made in the diagnosis and management of acute hematogenous osteomyelitis in children, with the publication of evidence-based clinical practice guidelines by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) [2][13][20]. These guidelines provide recommendations for the diagnosis, initial management, antibiotic selection, duration of therapy, and transition to oral antibiotics in pediatric acute hematogenous osteomyelitis [2][13][20]. Recent evidence supports shorter and narrowed antibiotic courses, with appropriate transition to outpatient oral treatment providing effective infection clearance and reduction in complications [2][13]. MRI has a crucial role in pediatric osteomyelitis, enabling the identification of even the earliest alterations previously not visible on imaging, and has become the preferred imaging modality for diagnosis [4][13]. Despite these advances, the management of pediatric osteomyelitis remains controversial, with no consensus among the approaches proposed by different guidelines, particularly regarding the duration of intravenous therapy and the timing of transition to oral administration [13].

Diabetic foot osteomyelitis (DFO) remains a particularly challenging form of bone infection, given the complex interplay of infection, ischemia, neuropathy, and impaired wound healing in the diabetic foot [8][18][19]. Recent advances in the management of DFO include the development of novel operative and nonoperative therapies, emerging biomaterials, local antibiotic delivery systems, and innovative surgical techniques [8][19]. The management of DFO mandates a comprehensive strategy that addresses both the infectious and surgical aspects of the condition, with antibiotic therapy guided by culture results playing a central role [18][19]. Bioactive glass has been used successfully in the treatment of multidrug-resistant osteomyelitis in diabetic foot, with case reports demonstrating the potential of integrating antibiotic therapy, conservative debridement, and bioactive glass to improve outcomes [8][20].

Prevention Strategies

The prevention of osteomyelitis encompasses both primary prevention—avoiding the initial development of bone infection—and secondary prevention—preventing recurrence in patients who have been successfully treated [19][25]. Primary prevention strategies include prompt and appropriate management of open fractures, including early antibiotic prophylaxis, thorough irrigation and debridement, and appropriate wound care [5][10]. In patients with diabetes, rigorous glycemic control, regular foot examinations, and prompt treatment of foot infections are essential to prevent the development of diabetic foot osteomyelitis [5][18]. For patients undergoing orthopedic surgery, perioperative antibiotic prophylaxis, meticulous surgical technique, and appropriate wound care reduce the risk of surgical site infection and subsequent osteomyelitis [5][15]. Secondary prevention focuses on the eradication of persistent infection and the prevention of recurrence, which requires complete surgical debridement of all necrotic and infected tissue, appropriate pathogen-directed antibiotic therapy for an adequate duration, and management of host factors that predispose to infection [2][10][14]. The recognition of intracellular bacterial persistence and biofilm formation as key mechanisms of recurrence has led to the development of strategies aimed at disrupting biofilms and eradicating intracellular reservoirs, though these approaches remain largely experimental [1][3][9]. Emerging biomaterials with antimicrobial properties unrelated to antibiotics, such as bioactive glass, represent a potential solution to the problem of antimicrobial resistance and biofilm-associated recurrence [7][8][20].

Discussion

The past decade has witnessed substantial progress in the understanding and management of osteomyelitis, with advances in diagnostic imaging, antimicrobial therapy, surgical techniques, and biomaterials contributing to improved outcomes [1][2][6][7]. The development of evidence-based clinical practice guidelines, particularly for pediatric acute hematogenous osteomyelitis, has provided a framework for standardized, high-quality care [2][13][20]. The emergence of biomaterial-based approaches, including bioactive glass and antibiotic-eluting scaffolds, offers the potential for one-stage treatment of osteomyelitis with combined infection control and bone regeneration [7][8][17][20]. However, significant challenges persist. Osteomyelitis remains a difficult-to-treat bone infection due to its high recurrence risk, complex surgical demands, and rising rates of multidrug-resistant organisms [1][12][15]. The ability of *Staphylococcus aureus* to form biofilms, survive intracellularly, and persist in bone tissue continues to frustrate treatment efforts and contributes to high rates of recurrence [1][3][9]. The optimal duration of antibiotic therapy, the role of oral versus intravenous antibiotics, and the indications for surgical intervention remain subjects of ongoing debate [2][6][13]. The management of special populations, including patients with diabetes, peripheral vascular disease, and immunocompromising conditions, presents particular challenges that require individualized, multidisciplinary approaches [5][8][18].

Future Research Directions

Future research should prioritize several key areas to further improve outcomes in osteomyelitis [1][13][20]. Comparative effectiveness studies are needed to define the optimal duration and route of antibiotic administration for different types and stages of osteomyelitis, particularly in the context of emerging evidence supporting shorter courses and oral step-down therapy [2][6][13]. The development of novel antimicrobial strategies targeting persistent intracellular organisms and biofilm-associated bacteria represents a critical priority, given the limitations of conventional antibiotics in eradicating these reservoirs [1][3][9]. The integration of biomaterial-based approaches into standard treatment protocols requires further evaluation through high-quality randomized controlled trials [7][20]. Research is also needed to address the prevention and management of osteomyelitis in special populations, including patients with diabetes, immunocompromising conditions, and prosthetic joint infections [8][18][19]. Finally, implementation science research is needed to facilitate the translation of evidence-based guidelines into clinical practice and to address the barriers to optimal care [2][13][20]. Based on the synthesis of current evidence, several recommendations can be made for clinical practice [2][5][6][14]. Early diagnosis is essential to prevent complications, and clinicians should maintain a high index of suspicion for osteomyelitis in patients with suggestive clinical features and risk factors [2][5]. MRI is the imaging modality of choice for early diagnosis and should be obtained when osteomyelitis is suspected [4][5]. Microbiological diagnosis should be confirmed by bone biopsy, as surface cultures are unreliable [5][11][14]. Antibiotic therapy should be pathogen-directed based on culture and susceptibility results, with the duration and route of administration guided by the type and severity of infection [2][14][15]. Surgical debridement is essential in chronic osteomyelitis and in cases with extensive bone necrosis or abscess formation [2][6][10]. A multidisciplinary approach involving infectious disease specialists, orthopedic surgeons, and radiologists is recommended for optimal management [6][14].

Conclusion

Osteomyelitis remains a formidable clinical challenge, characterized by complex pathophysiology, diverse clinical manifestations, and substantial morbidity if not diagnosed and treated promptly and appropriately. This comprehensive review has examined current knowledge regarding the pathophysiology, clinical manifestations, diagnostic evaluation, microbiological characteristics, contemporary therapeutic strategies, and recent advances in the prevention and management of bone infection. The pathogenesis of osteomyelitis is intimately linked to the unique virulence mechanisms of *Staphylococcus aureus*, including biofilm formation, intracellular survival, and disruption of bone homeostasis, which collectively explain the remarkable persistence and treatment resistance of this infection. Contemporary diagnostic approaches integrate advanced imaging modalities, with MRI representing the most sensitive technique for early detection, alongside microbiological culture and histopathological examination of bone biopsy specimens, which remain the diagnostic gold standard . Treatment paradigms have evolved substantially, with current evidence supporting shorter intravenous antibiotic courses followed by oral step-down therapy for uncomplicated cases, while chronic osteomyelitis mandates aggressive surgical debridement combined with prolonged pathogen-directed antimicrobial therapy. Recent advances in biomaterials, including bioactive glass and antibiotic-eluting scaffolds, offer promising adjunctive strategies that combine infection control with bone regeneration. Emerging understanding of intracellular bacterial persistence and the osteoimmunological mechanisms driving bone destruction has opened new avenues for targeted therapeutic intervention. The prevention and management of osteomyelitis require a multidisciplinary approach integrating the expertise of infectious disease specialists, orthopedic surgeons, radiologists, and microbiologists. Future research should focus on optimizing treatment duration and route of administration, developing novel antimicrobial strategies targeting persistent organisms, integrating biomaterial-based approaches into standard protocols, and addressing the prevention and management of osteomyelitis in special populations. As the evidence base continues to evolve, clinicians must remain vigilant in the early recognition and diagnosis of osteomyelitis, adhere to evidence-based guidelines for treatment, and embrace emerging therapeutic approaches that offer the potential for improved outcomes. By addressing the challenges identified in this review and implementing evidence-based best practices, healthcare providers can significantly improve outcomes for patients with osteomyelitis, reducing both the immediate morbidity and the long-term sequelae of this devastating bone infection.

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