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Review Article

Osteomyelitis: Recent advances in pathophysiology and therapeutic strategies

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ABSTRACT

This review article summarizes the recent advances in pathogenic mechanisms and novel therapeutic strategies for osteomyelitis, covering both periprosthetic joint infections and fracture-associated bone infections. A better understanding of the pathophysiology including the mechanisms for biofilm formation has led to new therapeutic strategies for this devastating disease. Research on novel local delivery materials with appropriate mechanical properties, lower exothermicity, controlled release of antibiotics, and absorbable scaffolding for bone regeneration is progressing rapidly. Emerging strategies for prevention, early diagnosis of low-grade infections, and innovative treatments of osteomyelitis such as biofilm disruptors and immunotherapy are highlighted in this review.

1. Introduction

Musculoskeletal infections, specifically osteomyelitis, create a substantial burden to the patient, treating physician and the health care system as a whole.[1] The definition of osteomyelitis is generally accepted as an inflammatory process of bone and bone marrow caused by an infectious organism(s) which results in local bone destruction, necrosis and apposition of new bone. The term osteomyelitis implies bone or joint infection.[2–4]

The occurrence and economic burden of osteomyelitis is staggering. The incidence of joint infection following arthroplasty (joint replacement) ranged from 0.3% to 2.4% for total hip arthroplasties (THA) and 1.0% to 3.0% for total knee arthroplasties (TKA), depending on the study series. The incidence of osteomyelitis is higher in cemented than in cementless arthroplasties.[5–8] The mortality after septic revision (18%) was six times higher than that of aseptic revision (3%).[9] A recent Nationwide Inpatient Sample (NIS) study with 235,857 revision THA (RTHA) and 301,718 RTKA procedures demonstrated that joint infection was the most common reason (25%) for RTKA and the third most common reason (accounted for 15.4%) for RTHA in the United States (U.S.). Average individual hospitalization costs associated with periprosthetic infection were $25,692 for RTKA and $31,753 for RTHA in the U.S. hospitals.[10] Accumulative costs for the individuals with bilateral joint infections or multi-stage revisions would be much higher.

The incidence of fracture-associated bone infection varies from 1.8% to 27% depending on the bone involved and the grade/type of fracture. Closed and Gustilo type-I open fractures have lowest rate of infection (1.8%), while severe high energy lower extremity open fractures have highest occurrence of infection (27%), with the tibia being the most commonly affected.[11–15] The overall incidence of bone infection may continue to rise due to multiple factors including improved diagnosis, increasing patient risk factors (*i.e.* diabetes), and increased needs for arthroplasties.[16,17]

A better understanding of pathophysiology of osteomyelitis is a key factor for development of better therapeutic strategies for this devastating disease. In this review article, we will focus on the recent advances in pathophysiology and novel therapeutic strategies for joint infection following arthroplasty and post-traumatic (fracture-associated) bone infections resulting from contaminated open fractures or open treatment of closed fractures. The information is derived from both clinical and experimental studies.

2. Pathophysiology of osteomyelitis

2.1. General pathophysiology

Osteomyelitis encompasses a broad spectrum of disease mechanisms with three generally accepted categories: hematogenous (blood borne) spread, contiguous contamination and vascular

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or neurologic insufficiency associated infection.[18] The characteristics of each category can be summarized as follows: (1) Primary hematogenous spread of bacteria mainly afflicts the metaphysis of skeletally immature patients or vertebral bodies at all ages, although infection at other locations may occur.[19,20] (2) Contiguous infection is usually spread from a contaminated site, most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with an orthopedic implant. (3) Vascular or neurologic insufficiency associated osteomyelitis results from poor blood supply, diabetic wounds, loss of protective sensation and altered immune defenses, commonly affecting the lower extremity (Fig. 1).[3,21,22]

Although all types of organisms, including bacteria, viruses, parasites, and fungi may cause osteomyelitis, bone infections are commonly caused by certain pyogenic bacteria and mycobacteria (in some countries). *Staphylococcus aureus* (*S. aureus*) is responsible for 80% to 90% of the cases of pyogenic osteomyelitis, while *Staphylococcus epidermidis* (*S. epidermidis*) is the most abundant skin flora which seems to predominately infect medical devices, including orthopedic hardware implants and catheters.[23,24]. More recently, Benito et al. reported a five-fold increase in the yearly occurrence of polymicrobial infections from 2004 to 2010, and an equally alarming increase in the yearly proportion of infections caused by gram-negative bacteria. Of these, Enterobacteriaceae are challenging because they resist a wide range of antibiotics.[25–27]

When bone tissue is infected, the bacteria induce an acute inflammatory reaction. The bacteria and inflammation affect the periosteum and spread within the bone causing bone necrosis. In children, the periosteum is loosely attached to the cortex, allowing for the formation of sizable subperiosteal abscesses along the bone surface. Lifting of the periosteum further impairs the blood supply to the affected bone causing segmental bone necrosis known as a *sequestrum*.[3] In the chronic stage, numerous inflammatory cells and their release of cytokines stimulate osteoclastic bone resorption, ingrowth of fibrous tissue, and the deposition of reactive new bone in the periphery. When the newly deposited bone forms a sleeve of living tissue around the segment of devitalized infected bone, it is known as an *involucrum*. Rupture of a subperiosteal abscess may lead to a soft-tissue abscess and the eventual formation of a *draining sinus*.[3]

2.2. Pathophysiology of periprosthetic joint infection

Periprosthetic joint infection (PJI) can occur at different times throughout the lifetime of an orthopedic implant, which can be classified into early (<3 months), delayed (3 months–2 years), and late (>2 years).[28] Early infections occur as a result of direct perioperative inoculation. Delayed infections can be caused by perioperative inoculation of a less virulent bacterium, or a hematogenous source. Late onset infections are more commonly caused by a remote infection that leads to hematogenous seeding of the implant surface or joint space by harmful bacteria. Poor host conditions could worsen this process.[25,28] Patients with a history of PJI had a greater risk of developing PJI in a subsequent THA or TKA.[29]

In 2011, the Musculoskeletal Infection Society proposed a unique set of PJI criteria, which were later revised at the International Consensus Meeting (ICM) on PJI. The diagnosis of PJI can be established if one of the following three major criteria occurs: two positive periprosthetic cultures with identical organisms; a sinus tract communicating with the joint; having three of the following minor criteria: (a) elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), (b) elevated synovial fluid white blood cell (WBC) count, (c) elevated synovial

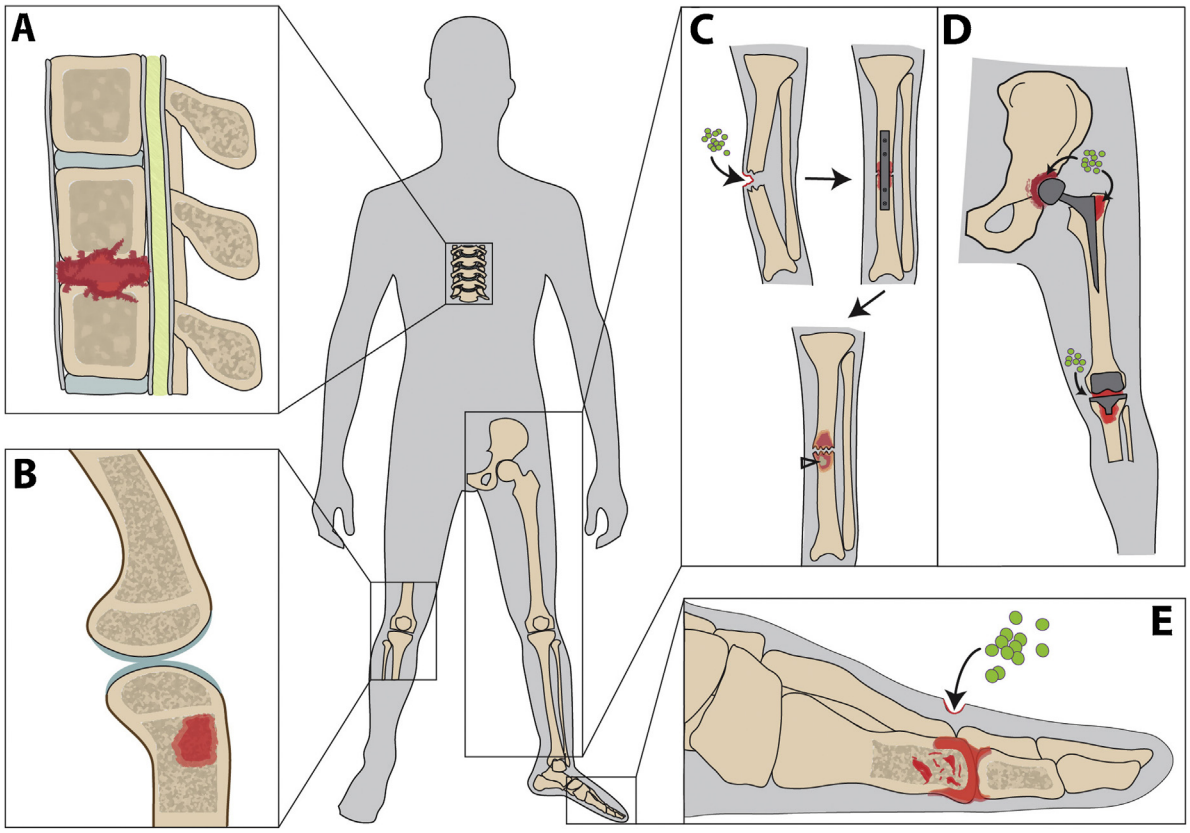

Fig. 1. A diagram showing three categories of osteomyelitis. (A and B) Primary hematogenous (blood borne) spread of bacteria mainly afflicts the vertebral bodies at all ages or the metaphysis of skeletally immature patients. (C and D) Contiguous bone infection is most commonly seen with direct contamination 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.