Orthopaedic device-related Infections in long Bones – The Management Strategies

Shyam Kumar Saraf¹, Aditya Malik¹

Abstract

Orthopedic device–related infections (ODRIs) present a unique scenario and a often challenging situation to manage. This review focuses on etiopathogenesis, classification, diagnosis and management of ODRI. The current literature has been reviewed and the inferences are combined with authors personal experiences to provide practical conclusions that can be used by the readers in clinical practice.

Keywords: Orthopaedic device related infections, management, surgical

Introduction

Despite considerable progress in prevention and management of implant-associated infection, the absolute number of patients with such infections is rising due to the lifelong risk for bacterial seeding on the implant. Infections associated with prosthetic joints are less frequent than aseptic failures, but represent one of the most devastating complications associated with high morbidity and substantial cost. [1-4]

Pathogenesis

Physiology of biofilm formation is the cornerstone for understanding the pathogenesis of orthopedic device-related infections. It involves interaction between microorganisms, the implant and the host. The first and most important step in biofilm formation is the ‘race to the surface’ of the implant between tissue cell integration and bacterial adhesion.[5] On contact, body fluids immediately coat all surfaces with a layer of host material, primarily serum proteins and platelets. Albumin is rapidly deposited on foreign material and prevents nonspecific neutrophil activation and deposition of matrix proteins on the surfaces. Adherence of Staphylococcus aureus to bioprosthetic materials is mediated by adhesins such as - fibronectin, fibrinogen, fibrin, collagen, laminin, vitronectin, thrombospondin, bone sialoprotein, elastin, and the matrix-binding protein. These host proteins promote attachment of S. aureus onto polymeric or metallic surfaces by specific receptors.[6.] Adherence progresses to aggregation of microorganisms on the surface of the foreign body, forming a biofilm. Thus biofilms can be defined as structured communities of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. Foreign bodies are devoid of microcirculation, which is crucial for host defense and the delivery of antibiotics. Existence within a biofilm represents a basic survival mechanism by which microbes resist against external and internal environmental factors, such as antimicrobial agents and host immune system [7]. These microorganisms live clustered together in a highly hydrated extracellular matrix attached to some surface. Depletion of metabolic substances or waste product accumulation in biofilms causes microbes to enter a slow growing or stationary state. Within biofilms, microorganisms develop into organized and complex communities with structural and functional heterogeneity resembling multicellular organisms in which water channels serve as a rudimentary circulatory system. Release of cell-to-cell signaling molecules (quorum sensing) allows microorganisms in a biofilm to respond in concert by changing their gene expression involved in biofilm differentiation [8]. Biofilm microorganisms, therefore, are significantly more resistant to killing by growth-dependent antimicrobials than their free-living counterparts. As a result, standard antibiotic therapy typically reverses signs and symptoms caused by planktonic bacteria released from the biofilm but fail to kill bacteria in the biofilm.

Classification of ODRI

Orthopedic device-related infections occur per-operatively by bacterial contamination of the surgical site during surgery or immediately thereafter, by hematogenous microbial spread through blood from a distant focus of infection, or continguously by direct or lymphatic spread from an adjacent infectious focus or penetrating trauma.

Prosthetic Joint Infections can be classified into three categories based on the duration and timing of appearance of symptoms post surgery.

1. Early Infections – Manifestation of infection at the implant site within 3 months post surgery. It occurs post operatively and
is generally caused by virulent organisms like Staphylococcus aureus. There is persisting local pain, erythema, edema, delayed wound healing or dehiscence, hematoma and/or fever.

2. Delayed Infections – Manifestation of infection 3 – 24 months after surgery. Mostly they are due to organisms of low virulence, for example, Coagulase negative staphylococci, Propionibacterium acnes. Persisting or increasing joint pain and early loosening are the hallmarks. Clinical signs of infection may be lacking and there, the most important differential diagnosis is aseptic failure.

3. Late Infections – Manifestation of infection more than 2 years after surgery. Most such infections result from hematogenous seeding from other foci, such as the skin, respiratory tract, urinary tract and/or dental foci[9,10].

In internal fixation devices, associated infections may again be classified into three categories based on the timing of manifestation symptoms post fixation.


2. Delayed Infections – Manifesting at 2–10 weeks post fixation.


Diagnosis of Infection
A combination of clinical, laboratory, histopathology, microbiology and imaging studies is required for the diagnosis of infection (ODRI). Early infection is usually easy to diagnose, as it presents clinically with both systemic and local signs. Systemic signs include fever, malaise, lethargy and loss of appetite. There may be erythema, edema, induration, raised temperature or even frank pus discharge at the operative site. Secretary wet wounds and unsatisfactory wound healing are common presentations. However, in cases of delayed and late infections, a high degree of suspicion is required. Short course of antibiotics may suppress the earlier infection to reappear later. Delayed or chronic infection may present as persistent pain at local site, local signs of inflammation or sinus. We often see sinuses/ discharges from interlock screw/ bolts or persistent discharging sinus in a plated fracture. Unusual delay in fracture healing, loosening of plates and screws should be taken as highly suspicious in favour of infection even if there may not be exterior signs of infection. Many a time patients present with broken/ bent internal fixation implants without any history of trauma. Ununited fractures due to infection should be strongly suspected in such cases. (Fig.1) Plain X-ray of the operative site may not contribute in the diagnosis in the initial post operative days. Later it may show the osteoporosis around fracture site. The signs of loosening of well fixed plate and screws, reaction around the screws, non union/ delayed union of fracture, sequestrum formation, reaction around the intra medullary nails are the radiological signs of infection. If infection is suspected clinically, even in the absence of radiological signs of infection, it is wiser to explore the wound and send the material for histology and
cultural and sensitivity. Blood leukocyte counts and differential counts may show leukocytosis and neutrophilia in acutely acquired infections, however, they are not sufficiently discriminative to predict the presence or absence of infection. Post surgery, C-Reactive Protein and ESR is acutely elevated and returns to normal within weeks. Therefore, preoperative and repetitive postoperative measurements are more informative than a single value in the postoperative period. In a prospective case-control study involving 58 patients, elevated serum Interleukin-6 concentration correlated with peri-prosthetic infection in patients undergoing re-surgery at the site of total hip or knee arthroplasty [12]. Synovial fluid leukocyte count represents a simple, rapid and accurate test for differentiating prosthetic joint-associated infection from aseptic failure. In prosthetic knee infections, synovial fluid leukocyte count of more than 1.7 x 10^9/l and differential of more than 65% neutrophils has a sensitivity for infection of 94% and 97%, and specificity of 88% and 98%, respectively [13]. Scintigraphy by means of a technetium (Tc99m) scan, gallium citrate (Ga67) scan, or indium (In111)-labeled leukocyte scan may be helpful in the diagnosis of ODRI. However, this approach is expensive, and the accuracy of these methods is still limited. Histopathological examination of the periprosthetic tissue has a sensitivity of more than 80% and a specificity of more than 90% [14]. Acute inflammation has been variably defined to range from at least 1 to 10 neutrophils per high power field. The degree of infiltration with inflammatory cells, however, may vary considerably between specimens from the same patient, even within individual tissue sections. Therefore, areas with the most florid inflammatory changes should be assessed and at least 10 high-power fields should be examined to obtain an average count [15]. Histopathology examination does not identify the causing organism, however, can confirm the presence of infection. Rarely Mycobacterium tuberculosis as the cause of infection has been reported. Aspiration of synovial fluid and operative site tissue cultures provide the most accurate specimens for detecting the causative microorganism. At least three operative site tissue areas should be sampled for microbiology. If possible, antimicrobial therapy should be discontinued prior to tissue sampling [16]. Peri-operative prophylaxis at revision surgery should not be started until after tissue specimens have been collected for culture [17]. If implant material is removed, the device can be cultured in enrichment broth media. The risk of contamination during processing, however, is high and the interpretation of the microbiologic result difficult [18]. New diagnostic approaches include sonication of removed implants to dislodge adherent microorganisms growing in biofilms and the use of molecular techniques to improve diagnostic yield. Explanted implants from 54 patients with aseptic failure and 24 with prosthetic joint infection were sonicated in polyethylene bags, the culture sensitivity of sonicate fluid was superior to that of standard peri-prosthetic tissue (75% versus 54%), whereas the specificity was 87% and 98%, respectively [19].

Treatment strategies
There is a trade-off between bony stability and foreign body response. Stability is necessary to eliminate the infection, but organisms remain adherent to the implant and cause persistent infection. If an implant is not necessary to maintain bony stability, it should be removed. Implants needed for stability should be retained until there is bony stability, or they should be replaced by another form of fixation (e.g., removing a plate and replacing it with an external fixator). If infections are not treated aggressively, surgical...
fixation becomes compromised. It is easier to treat a stable healed fracture with osteomyelitis than an unstable infected non-union. Thus, complete eradication of microorganisms in these infections is not always a mandate, as the colonized device can be removed after the bone is consolidated [20,21].

**Surgical strategies**

Depending on the type and susceptibility of pathogen, duration of symptoms, stability of the implant and the condition of the surrounding soft tissue, the surgical treatment modality may be chosen. The treatment includes debridement with retention of orthopedic device, (Fig.2 & 3) one or two stage exchange, permanent removal of the implant etc. Debridement with retention of implant is a reasonable option for patients if duration of manifestation is less than 3 weeks, the implant is stable and the soft tissue is in good condition, and an agent with activity against biofilm microorganisms is available [22-26]. The one-stage exchange designates the removal and implantation of a new orthopedic device during the same surgical procedure. This approach is recommended if the surrounding soft tissue is in good condition, the infecting pathogen does not belong to the difficult-to-treat microorganisms, and the patient has no severe co-morbidity [27–30]. The two stage exchange includes removal of the implant, with implantation of new device during a later surgical procedure. Typically a short interval until re-implantation (2-4 weeks) and a temporary antimicrobial impregnated bone cement spacer / beads or an external fixation device is used to secure the limb length. A longer interval (about 8 weeks) is preferred if the microorganism isolated is from the difficult-to-treat category. (eg. MRSA, enterococci or fungi). Permanent removal of device is usually reserved for patients with a high risk of re-infection, in the elderly or when no functional improvement after surgery is expected.

**Antibiotic treatment**

Intravenous treatment should be typically administered for the initial 2–4 weeks followed by oral therapy to complete the treatment course. In patients with two-stage exchange with a long interval (8 weeks), the aim of antimicrobial therapy is complete elimination of infection in the absence of any foreign material (e.g. antibiotic mixed spacer). Two weeks before re-implantation of the prosthesis, antimicrobial treatment is discontinued in order to get reliable tissue specimens for culture and histopathology at the time of re-implantation. In fracture- fixation devices, the treatment duration is 3 months with device retention, or 6 weeks with removal of all hardware [31,24]. If no antibiotic with efficacy on adherent bacteria is available, treatment with implant retention is generally only suppressive until the implants can definitively be removed. In such cases antibiotics should be continued for at least 2 weeks after removal of all implants to avoid development of chronic osteomyelitis. Many a times prolonged administration of systemic drugs may not be effective, hence the concept of local antibiotic delivery system has come up. The advantage is extremely high level of local antibiotic concentration. This facilitates delivery of antibiotics by diffusion to avascular areas of wound. The resistant organisms start responding to this high concentration. The local antibiotics can be delivered through Non degradable beads – PMMA beads / Spacers (Fig.4 & 5) or Bio degradable beads like bone graft, bone graft substitutes, natural polymers, synthetic polymers, composite biomaterials etc.

**Prevention of infection – The best strategy**

As noted from the above discussion, treatment of orthopedic device-related infections is a scenario where many variables play a role in deciding the treatment. The treatment however is difficult and prolonged. Therefore, the best treatment strategy is prevention of infection. Antimicrobial prophylaxis remains the single most
effective method of reducing the prevalence of infection after fracture fixation both. In bone surgery, a first- generation or second- generation cephalosporin, such as cefazolin or cefuroxime, is a rational choice. If the patient is allergic to cephalosporins, or in settings with high prevalence of methicillin resistant S. aureus (MRSA), vancomycin or teicoplanin are alternative options [32]. For optimal efficacy of the prophylactic agent, antimicrobial inhibitory concentrations must be achieved in tissue at the time of incision and last during the entire procedure. In an animal study, a short period of prophylactic efficacy of 3 hours has been observed. These animal data have been confirmed in a large retrospective study evaluating the outcome of 2847 surgical wounds [33,34]. When a tourniquet is used, tissue concentrations of the antibiotic are usually insufficient for prevention of surgical site infection when administered 5 min before inflation or later. For internal fixation devices of closed fractures in centers with infection rates of less than 5%, a single dose of intravenous cefuroxime is a reasonable option. In centers with unknown or high infection rates (>5%) and in open fractures grade I and grade II, a 1-day prophylaxis is preferred: intravenous cefuroxime and/or tazobactam-piperacillin maybe be used. In patients with internal fixation of grade III open fractures, pre-emptive therapy with an anti staphylococcal drug such as intravenous amoxicillin/clavulanic acid or cefuroxime may be used. In patients with internal fixation of grade III open fractures, pre-emptive therapy with an anti staphylococcal drug such as intravenous amoxicillin/clavulanic acid or cefuroxime is a reasonable option.

Most infections with use of internal fixation devices are exogenous in peri operative period. There is no substitute for meticulous pre operative assessment and observing the rigorous protocol and discipline throughout the peri operative period. Hematogenous seeding of implants may occur during the whole life, although the risk of infection is highest in the first year after implantation. In a cohort study of 40 consecutive episodes of prosthetic knee infection, the fraction of hematogenous infections has been estimated at 38% [35]. The most frequent sources of hematogenous infection are infections of the skin and soft tissues, oral cavity, urinary and respiratory tract [36]. They must be tackled accordingly.

## Conclusion

The various problems in the management strategies are biofilm formation, bacteria are difficult to culture, the culture & sensitivity is not always reliable, oral and parental antibiotics may not resolve the basic biofilm nidus of infection, the immune response of patient may not be effective, adjoining joints have stiffness and finally the surgeon & patient both become impatient, tired, devoid of resources & their savings. The important factors for consideration in the management are; interval between surgery and clinical presentation of infection, severity of infection, identification of organism and stability at fracture site by the implant. Internal fixation device infection can be classified on the basis of time interval between surgery and clinical manifestations. Infection appearing within 3 weeks is usually as a result of Staph. aureus. Mild superficial infection like stitch abscess can be managed by IV antibiotics, however, in all other cases, it is safer to open the wound, drain abscess if any, debridement of dead necrotic tissue, granulation tissue, sending the material for C/S and wound irrigation. Removal of implant is not necessary at this stage, however, checking the stability of fracture by implant is important. Reinforce the stability if necessary. For deep delayed infection, open the fracture site, debride, irrigate and then local antibiotic beads can be put temporarily. Stabilize fixation if necessary. For mild delayed infection in intra medullary nailing, one can remove intra medullary nail followed by reaming and thorough lavage of canal. Depending upon the severity, one can reinsert another simple nail of higher diameter or antibiotic coated nail with or without bone grafting. In severe infection, it is safer to remove the nail, ream and putting temporarily antibiotic mixed cement coated intramedullary implant as first stage. Alternatively fracture can be stabilized temporarily by external fixator. In 2nd stage, with control of infection, debride again, ream the canal and put larger size of nail. Treatment of implant-associated infection requires prolonged antimicrobial therapy. The choice of the antimicrobial regimen depends on duration and pathogenesis of infection, stability of the implant, antimicrobial susceptibility of the pathogen, and condition of the surrounding soft tissue.

## References

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