

Infection in fracture fixation: Can we influence infection rates through implant design?

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Abstract Musculoskeletal infection is one of the most common complications associated with surgical fixation of bones fractured during trauma. These infections usually involve bacterial colonisation and biofilm formation on the fracture fixation device itself, as well as infection of the surrounding tissues. Antibiotic prophylaxis, wound debridement and postsurgical care can reduce the incidence of, but do not prevent, these infections. Much research and development has been focussed on ways to further reduce the incidence of infection and in the following short review we describe our experiences investigating the contribution of the basic design of fracture fixation devices on the susceptibility to infection. It has been shown in animal studies that device size, shape, mode of action and material and topography play an interrelated role in the susceptibility to infection. Although direct extrapolation from animal studies to the clinical setting is difficult, close consideration of the design factors that can reduce the incidence of infection in animal models is expected to help minimise the incidence of infection associated with any clinically implemented fracture fixation device.

1 Introduction

One of the most common complications associated with the surgical fixation of orthopedic fractures is the development of musculoskeletal infection, which commonly present

either within the first two post-operative months or many months to years post-surgery when a delayed or late developing infection is observed [1]. They are characterized, in the most severe of cases, by bacterial colonization and biofilm formation on the implanted device and infection of the adjacent tissues [2]. Growing as a biofilm on the surface of the implanted device, the bacteria are much more resistant to antibiotics [3, 4] and this means the infection can persist despite even aggressive antibiotic treatment. Fracture healing can be delayed or prevented and implant loosening can be observed as a consequence of the infection, and so to achieve a successful treatment outcome and allow fracture healing, surgical removal of the device is often required in addition to prolonged courses of antibiotic therapy.

Orthopedic procedures as a whole, including all fracture types and fixation techniques as well as prostheses, are associated with an average infection rate of 5% in the US, equating to 100,000 infections per year costing 15,000 US\$ per incidence [5]. The significant costs involved has driven much research into the prevention of these infections and much of this research has centered on the local delivery of antimicrobial agents, such as antibiotic loaded device coatings [6] and antibiotic loaded cements [7]. The use of these antibiotic loaded fracture fixation devices has been successfully proven to be effective in animal and clinical trials [6] and may be expected to become even more commonplace in future years. However, with the observed increase in antibiotic resistant organisms in the healthcare setting, the use of antibiotic loaded devices may not be used routinely for all fracture fixation procedures in the future. The majority of fracture fixation procedures are currently performed using standard, uncoated metal implants, usually electropolished stainless steel (EPSS), titanium or titanium alloys. A certain percentage of these cases will invariably develop infections

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despite best clinical practices, with the primary risk factors being the initial trauma, anatomical location of the fracture, extent of soft and hard tissue damage, whether there is an open or a closed wound [8–11] and any patient co-morbidities. In general, greater hard and soft tissue damage and an open wound are the greatest risk factors for the development of infection and adequate wound debridement and appropriate antibiotic prophylaxis [12] are required to minimise the incidence of early developing perioperative infections. The surgical approach, the fixation device used and further, the design of the chosen fracture fixation device and its application can influence the susceptibility to infection in addition to the obvious crucial role in fracture healing. The role of implant design on susceptibility to infection is the focus of the present paper.

2 Methods

For over 20 years orthopaedic devices and surgical techniques have been assessed in vivo with respect to influence on infection resistance at the AO Research Institute Davos. During this time at least eight separate in vivo studies have been performed assessing a range of fracture fixation devices, surgical techniques and antibiotic device coatings [13–20]. The animal models used to assess the likely incidence of infection usually involve early developing perioperative contamination models. Infections associated with implanted fracture fixation devices can also develop months or even years after the insertion of the fracture fixation device but these infections are less clearly understood and good animal models of these infections are lacking. Animal models of perioperative infection are, however, readily available and these have been used in conjunction with numerous orthopaedic fracture fixation devices to investigate which design features of the implanted device can influence the susceptibility to the development of an infection.

The methodological approach we use to assess the susceptibility to infection of fracture fixation devices minimises the number of experimental animals required to yield statistically significant results and yet gain maximum information about the performance of each device. This is an “up and down” dosage methodology and using this procedure the performance of each new device is evaluated at a range of inoculated doses spanning a low inoculum incapable of causing an infection and a higher inoculum resulting in infection in all animals. Differences in performance of each device may be observed at these doses, however, the greatest differences are expected to occur at the point where 50% of the animals develop an infection, and this is known as the ID₅₀ or Infectious Dose 50. After an initial dose finding study using as few animals as possible,

a greater number of animals are inoculated at the doses spanning the expected ID₅₀. This technique minimises the number of animals at less relevant doses, and increases the number of animals at the most relevant doses. A clear benefit of this methodological approach is that at the completion of this process the device is thoroughly evaluated at numerous doses, rather than at one single dose, which reveals the full difference in performance the tested devices.

The choice of organism, and further, the strain of that organism used in an animal infection study will have a large influence on the outcome and the interpretation of results. Usually an infection study will utilize *Staphylococcus aureus*, the organism most commonly isolated from fracture fixation device associated infections [21]. The complex clonal nature of the most prevalent organisms isolated from implant-associated infections has been revealed by molecular epidemiological studies [22–24] and this has provided much needed direction in the choice of bacterial strains for studies assessing resistance to infection of devices. It is now possible to ensure reference strains are selected that are representative of the types causing the largest number of clinical infections rather than strains that may be representative of a small fraction of clinically relevant infections [23, 24].

3 Results

The primary aims of any fracture fixation procedure are to restore pain free mobility, load bearing and to allow fracture healing. As modern fracture fixation devices have evolved over the decades numerous designs have been developed and tested with the aim of achieving these goals. In parallel to improved fixation it must also be considered that any new implant design could also have considerable influence on the susceptibility to infection. Therefore, many devices have been subjected to infection studies to determine the resistance to infection of these new implants, and it is from these studies that the design features of a fracture fixation device that make it more or less susceptible to infection have been identified, even though many of these design features are not primarily designed to reduce the incidence of infection.

The evolution of the standard AO fracture fixation plate has encompassed devices with varying modes of action in the past decades from the dynamic compression plates (DCPs), through to point contact fixators (PC-Fix) and the more recently developed locking compression plate (LCP) [25]. These devices have been developed to improve fracture healing and also to reduce soft tissue and vascular damage but also it has been found that these devices have quite different susceptibilities to infection attributed to changes in the mode of action of the plate designs. The

DCP provides fixation by compression of bone fragments across the fracture gap and also compression between the plate and the underlying bone across a large footprint. The large area of compression results in compression induced restriction of blood flow to the periosteum and in the bone leading in some cases to tissue necrosis. Any necrotic tissue lying beneath a DCP not only damages the periosteum and potentially delays healing, but it is also a recognised weak point for the development of infection. In later designs, the compression plate was replaced by an LCDCP (lower contact compression plate) with a smaller area of compression on the bone and a lower amount of damage to the periosteum. This was also developed further to a point contact fixator (PC-Fix), which reduces the area of contact between the plate and bone, functioning as an internal fixator and minimising the damage caused to the periosteum even more. The greater protection of the periosteum provided by the PC-Fix, leading to greater viability of tissues was predicted to improve fracture healing by reducing tissue necrosis, but also to improve resistance to infection in comparison with DCPs by the same mechanism. In an animal infection model the PC-Fix was indeed found to display a significant improvement in infection resistance over the DCP and this was attributed to improved viability of tissues [14]. This is a clear example of how improving implant design can significantly improve resistance to infection.

The material and the topography of any fracture fixation device is a factor which is known to influence the tissue response [26–31] and must also be considered as a potential influence on the development of infection. Of the commonly available orthopaedic implant materials stainless steel and titanium; stainless steel is associated with an increased infection rate in comparison with titanium for dynamic compression plates and intramedullary nails in animal models [13, 16] and also clinically for external fixation pins and spinal implants [32, 33]. This observation is commonly attributed to two factors; the improved biocompatibility of titanium over stainless steel and the increased observation of fibrous capsules around EPSS implants. The fluid filled fibrous tissue capsule that is often observed to form around the EPSS implant is not vascularised and is inaccessible to local immune defences thus providing a weak point for the propagation of infection [2, 34]. Improved adhesion of tissue to titanium over EPSS has been proposed to be the reason for the reduced prevalence of capsule formation around titanium implants in comparison with EPSS implants.

However, in comparing steel with titanium it must be recognised that steel is usually electropolished to a smooth surface, whereas titanium in its standard form has a microrough surface. Therefore, when comparing steel with titanium, there is a material difference, but also a

topographical difference and for the majority of animal models of orthopaedic device related infection, where smooth steel is compared with rough titanium, a clear contribution of surface topography, that can be separated from material, on infection rate cannot be determined [13, 16]. The microrough surfaces of titanium fracture fixation devices encourage tissue adhesion. Once integrated with the tissues, the devices are much more resistant to bacterial colonisation [2]. However, in certain clinical situations tissue integration is not desired. This is the case for example when excessive bone adhesion complicates implant removal, or soft tissue adhesion impairs limb function, for example tendon adhesion after fixation of distal radius fractures [35, 36]. As a solution to these problems, polishing screws, internal fracture fixation plates and intramedullary nails composed of commercially pure titanium (cpTi) and titanium aluminium niobium (TAN) has been found to reduce tissue adherence *in vivo* in comparison with standard equivalents [26, 30, 31] and thus has significant potential clinical benefit in reducing removal complications, operative time or improving limb function. However, it is clear that altering implant surface topography to ease implant removal could also alter the resistance to infection through modifying both bacterial and potentially host cell adhesion. Studies *in vitro* have shown that bacteria adhere in a different rate to commonly available implant materials dependent on topography [37–39], and *in vivo* studies have shown that the smooth surface of the steel implants can lead to capsule formation which is a recognised risk factor for the development of infection.

We recently isolated the contribution of topography on resistance to infection for LCPs. The LCP, which is a further development of the PC-Fix, protects the periosteum when in locking mode and thus an improvement in infection resistance is expected to be gained. Currently, LCPs are also most commonly available as standard microrough cpTi or smooth EPSS. When the standard implant materials EPSS and cpTi were evaluated, we found that there was no large difference in infection resistance, with only a small difference in ID_{50} between the cpTi and EPSS LCPs (Fig. 1). At this point it is important to highlight the contrast with the previous animal studies where EPSS was found to have increased infection rates and a ten fold or greater increase in ID_{50} in comparison with standard cpTi when the DCPs were evaluated. In comparing the results of our LCP study to the DCP study [13], it must be considered that the improved biological protection of periosteum provided by the LCP is believed to be the reason why the previously observed differences in infection susceptibility experienced for EPSS and cpTi DCPs is not observed for the LCPs in our animal model. When we compared polished titanium with polished steel *i.e.* when the topography was identical with (LCPs), we found that there remained no

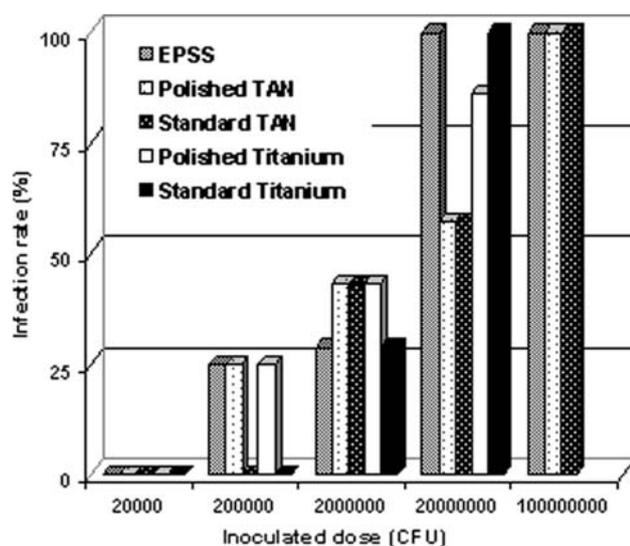


Fig. 1 Infection rate of standard and polished LCPs of titanium and TAN in comparison with EPSS controls at the various bacterial inocula

difference in infection susceptibility. Therefore, polishing which has previously been shown to ease implant removal, by prevention of bony integration and to prevent gliding tissue damage, could be clinically implemented with locking plates and screws, since we show that it does not reduce infection resistance. Overall these studies would suggest that in optimal conditions there should not be a major difference between device related infection with regards to either material (EPSS or titanium) or its topography, though in compromised situations with compression fixation titanium and its alloys have a clear advantage, with regards to infection, over EPSS.

In the context of intramedullary nails, which occupy a completely different biological environment to the plates, implant design also plays a role in the susceptibility to the development of an infection. Insertion of a guide wire to help align fractured bone fragments and aid nail insertion requires a continuous conduit through the nail. Therefore, hollow and cannulated nails have been developed which allow insertion of the guide wire; however, this design incorporates a dead space in the centre of the nail, which is predicted to negatively influence susceptibility to infection. In the animal study designed to test nail design, a decreased resistance to infection was indeed observed for the hollow nail in comparison with solid nails [16]. The solid nails do not create any dead spaces within which infecting bacteria can initiate and propagate infection and despite the benefits associated with the ability to utilise a guide wire, the increased susceptibility to infection is one contraindication to the use of a hollow nail, at least from the evidence of the animal model performed.

When the influence of material and topography was assessed for intramedullary nails, there was found to be no

difference in infection susceptibility between smooth TAN nails and standard TAN nails (unpublished results). Smooth TAN nails have been shown in animal studies to ease implant removal complications and so are expected to have significant clinical impact in certain application [40]. The control group EPSS was also shown to have a similar influence on susceptibility to infection in comparison with both the smooth and standard TAN intramedullary nails. Therefore, overall for the nail studies, it has been shown that material and topography can play a limited role in susceptibility to infection, and that the main design features improving resistance to infection is the lack of the creation of dead spaces [16].

4 Discussion

In the context of orthopaedic fracture fixation devices it must be remembered that it is difficult to directly extrapolate the data from animal models to the clinical situation. Nevertheless, the factors which are found to influence the susceptibility to infection of a particular device in an animal model are expected to play some role in the clinical situation. The features with potential to influence the susceptibility to infection of a particular device include; material, biocompatibility, topography, surface area available for colonisation [17], the creation of dead spaces [17], bone contact and compression causing necrosis [14] and the stability provided by the implant [41]. The animal data shows that minimising dead spaces and protecting the viability of the tissues in contact with the implanted device are expected to have the greatest influence upon the susceptibility to infection. Implant material and topography will also play a role, although experiences to date suggest that protection of the viable tissues may be even more important.

In general, the incidence of infection can be most effectively minimised by paying attention to the recognised need to remove all dead necrotic tissue at the time of surgery and adequate antibiotic coverage, nevertheless, the role of the design of the implant should not be neglected and in using implants that protect the viable tissues and through performing surgery that creates minimal unnecessary damage to the intact, viable tissue, device related infection is expected to be minimised.

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