Doctoral thesis summary of Dr. Willem-Jan Metsemakers

Over the past decades, the treatment of (poly)trauma patients has changed dramatically. The transition to damage control surgery (DCS), for example, has led to a decrease in morbidity and mortality over the past decades, and is an excellent example of how preventive measures have improved the care of these patients. Aside from DCS, other interventions have also improved the care of the injured patient. However, some important issues remain. Musculoskeletal complications, like implant-related infections and compromised fracture healing, are currently the most important causes for a negative outcome in trauma patients overall. These sometimes complex problems lead to impaired limb function, even in the hands of experienced trauma surgeons. Furthermore, they place a cost burden on total healthcare expenditure. Better understanding of the epidemiology and pathogenesis of these complications is essential because this can lead to prevention rather than treatment strategies. Chapter 1 gives a historical overview of the treatment of polytrauma patients, followed by an introduction to the problems regarding these complications that we are facing today.

The surgical approach, the fixation device used, and further, the design of the chosen fracture fixation device and its application can all influence the susceptibility to musculoskeletal complications. As explained in the literature review in Chapter 2, our understanding of the impact of biomechanical stability on fracture healing and infection has evolved over the past decades. It is now realized that fracture stability is of paramount importance not only for achieving fracture union but also for infection prevention and treatment. Furthermore, the influence of the implant on the outcome in fracture care has been described. Over time, different models were created, from the dynamic compression plate (DCP), the limited contact DCP (LC-DCP), through to point contact fixator (PC-Fix), and more recently, the locking compression plate (LCP). These devices have been developed to improve fracture healing and reduce soft tissue and vascular damage. It has also been found that these devices have quite a different susceptibility to infection, by reducing the area of necrosis in contact with the bone. Chapter 2 further focuses on the differences between the most widely used metal implants today: usually stainless steel, titanium, or titanium alloys (TAN). All these materials offer a good combination of desirable mechanical properties and biocompatibility. Finally, with respect to implant-related infections, research focuses on biofilm forming bacteria. Most antimicrobial agents have a limited efficacy against biofilm infections; therefore, novel preventive and therapeutic options are needed. Local delivery systems, such as implant coatings, could be an asset in this field.

Chapter 3 describes the clinical studies that retrospectively identified different risk factors for complications after intramedullary treatment of diaphyseal long bone (humerus, femur and tibia) fractures. It is clear that the region of the tibia is especially prone to complications, although it has to be stated that nonunion is also frequent after the occurrence femoral shaft fractures. Polytrauma patients seem at risk for nonunion after the intramedullary treatment of tibia shaft fractures. Furthermore, statistically significant longer hospitalization periods can be noted for this patient population, especially after the treatment of femoral shaft fractures. Im-
plant-related infection is predominant in the tibia shaft fracture population. Complications in patients with humeral shaft fractures are less frequent. Consequently, preventive measures should focus initially on lower extremity fractures.

In Chapter 4 the results are shown of preclinical research using different rabbit models. The objective of the first study was to provide definitive data on the role of implant material and surface topography in the development of infection in a clinically relevant rabbit fracture model. As mentioned in the literature review (Chapter 2), the metals predominantly used in fracture care today are stainless steel, titanium and titanium alloys. The results in this study did not show a statistical significant difference in infection susceptibility between the different metals. The finding that standard titanium had a lower bacterial burden compared to stainless steel, but only when using a high bacterial inoculate, is interesting and indicates that material may not influence the infection risk, but rather the infection severity. In theory the high bacterial load mimics open fracture cases, where the use of titanium implants could be considered a potential benefit. Furthermore, polished titanium implants with the potential to reduce complications associated with tissue adherence are not expected to affect the infection rate, nor the influence on implant stability. The second preclinical study in Chapter 4 focused on improved infection prophylaxis by providing local delivery of antibiotics directly to the tissue-implant interface in a non-fracture rabbit model. The antibiotic of choice was doxycycline as it has a low resistance to the most commonly encountered microorganisms causing implant-related infections, including MRSA. It was incorporated into a biodegradable Polymer-Lipid Encapsulation Matrix (PLEX)–coating. The PLEX-doxycycline coating provided complete protection against implant-related MSSA infection, and resulted in a significant reduction in the number of culture positive samples when challenged with a doxycycline-resistant MRSA.

Chapter 5 focuses on a clinical preventive model of implant-related infection in high risk patient populations by using an antibiotic-coated implant. At the time of the study, the only available trauma related implant on the European market was a gentamicin coated intramedullary tibia nail (Expert Tibia Nail (ETN) PROtect™). In our patient population, no implant-related infections occurred after placement of the gentamicin coated nail. Following this study and a literature search, antibiotic-coated implants seem to be a potential option for prevention of infection in trauma patients. In the future this statement needs to be confirmed by large randomized clinical trials.

Chapter 6 discusses the epidemiology of long bone fractures, but also the functional and socio-economic impact of musculoskeletal complications after the treatment of these fractures. Especially in the field of implant-related infections, musculoskeletal trauma research lags behind orthopaedic arthroplasty research. There is a lack of data regarding the definition, functional outcome and healthcare burden of implant-related infections in fracture care. Future clinical research will need to address this issue. Furthermore, the emergence of antibiotic-resistant bacteria, particularly MRSA, has become a significant global healthcare issue that has also influenced trauma medicine. Antimicrobial peptides (AMPs) could be a possible posi-
tive future perspective. Finally, local delivery systems, such as implant coatings and hydrogels, seem to be a potential option for infection prevention and treatment.

**Publications related to the doctoral thesis of Dr. Willem-Jan Metsemakers:**


