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Daniël Janssen

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Daniël Maria Carolus Janssen
Born 28 February 1982, Eys

Supervisors:
Prof. Dr. P.C. Willems, promotor
Prof. Dr. L.W. van Rhijn, promotor
Dr. J.A.P. Geurts, co-promotor

Assessment Committee:
Prof. Dr. P.H.M. Savelkoul, Hoogleraar Medische Microbiologie, UM (voorzitter);
Prof. Dr. H. van Santbrink, Hoogleraar Spinale Neurochirurgie, UM;
Prof. Dr. R.R.W.J. van der Hulst, Hoogleraar Plastische Chirurgie, UM;
Prof. Dr. P.C. Jutte, Hoogleraar Orthopedie, Universitair Medisch Centrum Groningen;
Prof. Dr. L. Moke, Hoogleraar Orthopedie, Universitair Ziekenhuis Leuven, België.

Aan mijn ouders en aan Savi en Milas

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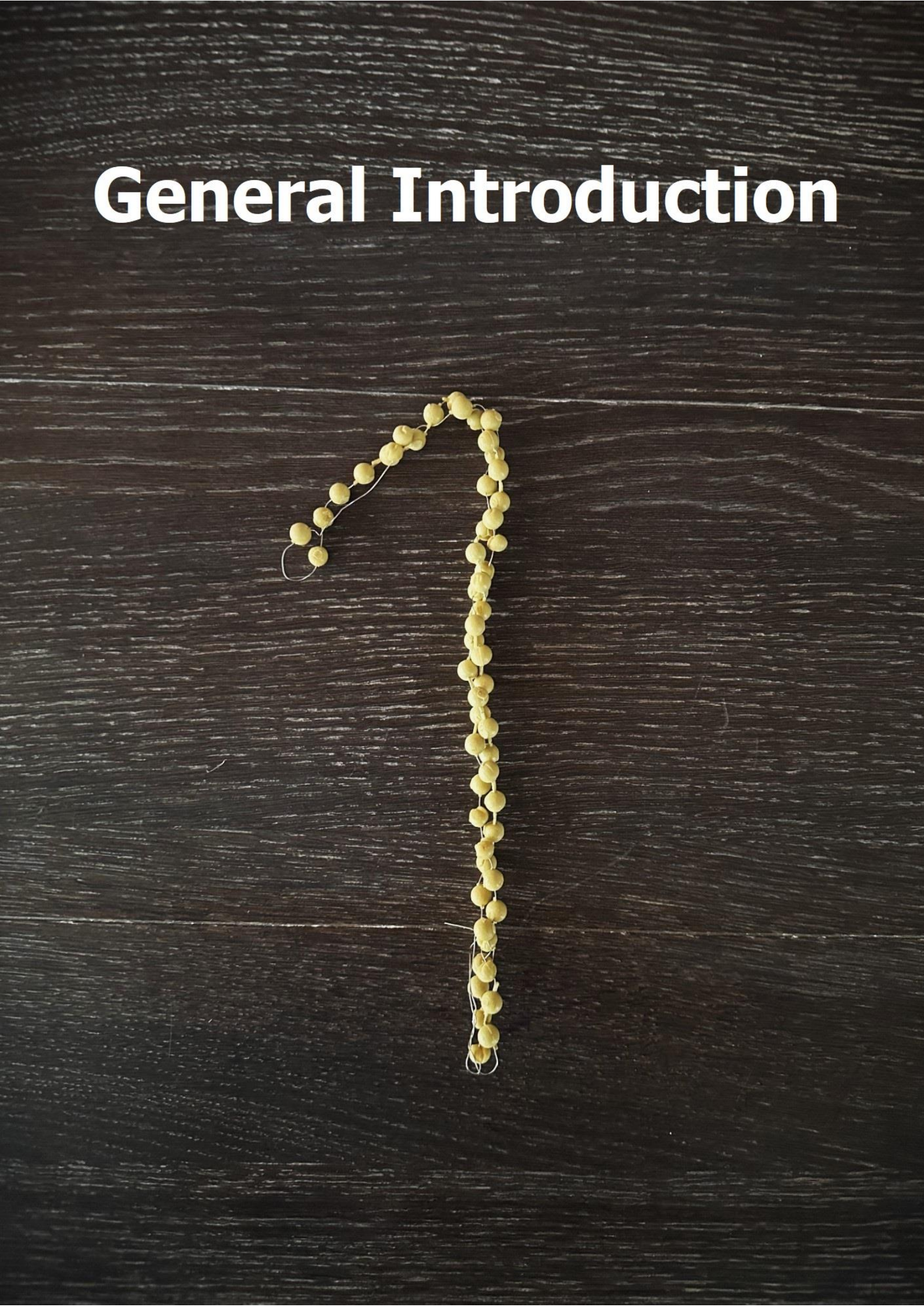

Chapter I

General introduction

Osteoarthritis (OA) is the most common joint disorder. Among adults 60 years of age or older the prevalence of symptomatic knee OA in the Westerns society is approximately 10% in men and 13% in women. The number of people affected with symptomatic OA is likely to increase due to the aging of the population, sedentary lifestyle with deficits in muscle strength and the obesity epidemic.(1–5)
Pain from OA is a key symptom in the decision to seek medical care and is an important reason for disability. OA is the 11th cause of disability in the world. It is responsible for activity limitations, particularly walking, and affects societal participation and quality of life. Patients with OA are at greater risk of all-cause mortality, particularly for cardiovascular diseases, than the general population. The rapid increase in the prevalence of this already common disease suggests that OA will have a growing impact on health care and public health systems in the coming decades.(1–3)

Total joint replacement has been shown to be a highly effective treatment for end-stage OA of the major weight-bearing joints. Health services are experiencing an exponential global rise in numbers of lower limb arthroplasty procedures performed for an ageing population. The incidence of joint replacement procedures performed each year in the United States is over 2.5 million total hip and total knee replacements.(6)

In the US the primary TKA volume will increase 139% and primary THA volume will increase 176% from 2019 to 2040 and increase 469% for TKA and 659% for THA to 2060.(7)

Over the last 10 years, the LROI (national register for joint arthroplasty in the Netherlands) witnessed a growth of total hip (THP) and total knee arthroplasty (TKP) procedures by 1300 cases/year for THP (from 23000 to 36000) and 600 cases/year for TKP (from 20500 to 26500) (LROI 2021).

Low back pain (LBP) is also a major health problem in developed countries and the leading cause of disability worldwide.(4,8) Reported LBP prevalence rates range from 4% to 69% and vary depending on the length of time evaluated (e.g., lifetime, 1-month and point prevalence) as well as pain intensity.(8-10) LBP causing patients to seek medical care has reported prevalence rates ranging from 4.5% to 32% and has been shown to be influenced by the length of time of symptoms, gender and race/ethnicity.(4,11)
The treatment of chronic low back pain can be challenging. In 80% to 95% of the patients a specific cause of the symptoms cannot be identified despite the existence of modern imaging techniques. However, in patients with a specific cause for their low back pain, such as a fracture, deformity or spondylolisthesis, operative treatment can be very effective.

Spinal fusion is a surgical procedure in which two or more vertebrae are fused rigidly to establish bony union, and which can be an effective treatment for specific spinal disorders. The first spinal fusion procedures were performed in 1911 in the United States by Hibbs and Albee to treat scoliosis and tuberculosis. In the last decades, the indications for spinal fusion have evolved and currently include scoliosis, kyphosis, vertebral fractures, tumors and degenerative conditions such as spondylolisthesis.(12)
Spinal fusion nowadays is achieved by instrumentation with implant material (cages or screws and rods) and a bone graft for definite bony fusion.
The number of patients undergoing spinal fusion procedures has increased tremendously the last decades with more invasive, complex procedures, younger patients and more revision procedures.(12–15)

Because orthopaedic procedures with total joint prosthesis and instrumented spinal fusion have shown good results, with an increase of quality of life, a further increase of these procedures in the coming decades is expected, with more aged patients, more revision procedures, but also more younger patients who will undergo these procedures (LROI 2021).(14,15)

Unfortunately, orthopaedic implants have a risk for bacterial infection. In literature the incidence of surgical site infection (SSI) after spinal surgery ranges from 2 to 12%, depending on diagnosis, surgical approach, use of spinal instrumentation, and the complexity of the procedure.(16–18) The incidence of prosthetic joint infection ranges between 1-2% in literature, and may be increasing just as the incidence of SSI after spinal surgery.(19)

Even if the incidence rate of implant infections remains unchanged, the prevalence of implant infections will increase, with the increasing number and more complex orthopaedic implants procedures. It has been predicted that infection will become the most frequent mode of failure of total knee and hip arthroplasty.(20–23) In 2020 infection was the first reason for revision surgery in the Netherlands for THP (24.3%) and second reason for revision surgery in TKP revision (23.3%) after instability (26.3%) (LROI 2018).

Route of infection

Considering orthopaedic implant infections, there are three possible routes of bacterial contamination.

- The first one is exogenous spread of the patient's own bacteria or microorganisms belonging to the operating personnel or the environment of the operating room during the perioperative period. These infections acquired in this perioperative period and can be split up into an acute and chronic manifestation. The difference of an acute or chronic manifestation is important for the choice of treatment and the chances for successful eradication of infection.
  Although there is no consensus on the exact postoperative time interval or a classification system for infected implants, an acute postoperative infection is diagnosed within 2-3 months of the index operation (primary or revision). Chronic infections presents with symptoms after more than 2-3 months of the index operation.(24)
- The second route is haematogenous spread of bacteria occurring postoperative from a confirmed source of infection elsewhere in the body, to a previously well-functioning implant. Haematogenous infection only plays a minor role in orthopaedic surgery with a proportion of all infections of 6-11%.(25) In literature this infection is often noted as an acute haematogenous infection with a short duration of symptoms, but a clear number for this duration is never been given.(26)
- A third route of infection is by colonisation as a result of direct contact with a neighbouring infected site, e.g. osteomyelitis, or diffusion through neighbouring tissues from outside the body, e.g. in the case of an infected wound or haematoma or diabetic ulcer.

Biofilm

Bacteria can exist as two different life forms. First, a planktonic (free-floating) form, metabolically active, rapid replication. Second form is in a biofilm.

Infections that are associated with a joint prosthesis are typically caused by microorganisms that grow in a biofilm.(27,28) These microorganisms live clustered together in a highly hydrated extracellular matrix of polymerised exopolysaccharide attached to a surface. A mature biofilm comprises up to 25-30% bacteria and 70-75% amorphous matrix.

The tolerance of the body towards an implanted foreign material (prosthesis or instrumented spinal fusion) is expressed by growth of host tissue around or on the surface of the implant. The principle of timely adherence of host cells or bacteria on the implant surface is known as "the race for the surface" **(figure 1)**.(28) This hypothesis postulates that when the surface of an implant is occupied by host tissue cells (before bacterial adhesion to that same surface), the implant surface would be less susceptible for bacterial colonisation.(28–30)

In healthy aseptic situations, the host cells (osteoblasts) adhere to the surface of the orthopaedic implant and start to proliferate and differentiate with the production of a collagenous matrix. The calcification of this matrix (carried out by osteoblasts) will eventually result in bone apposition on the implant surface.(31) However, in the case of unfortunate septic conditions, bacteria will settle on the implant surface, encapsulating themselves in a biofilm.

Nonspecific factors as surface tension, hydrophobia and electrostatic forbs and specific adhesins such as autolysin, extracellular DNA and staphylococcus surface protein 1 and 2 are providing adherence of microorganisms like s. epidermidis to the surface of an implant.(32) After this initial phase of adherence an accumulative phase is followed in which the microorganism cells adhere to each other and form the biofilm. This process is mediated by the polysaccharide intercellular adhesion.

Other microorganisms such as Staphylococcus aureus are more depended on interaction with host proteins, such as fibronectin, fibrinogen, and collagen. These proteins covered the orthopaedic implant immediately after implantation and the microorganism adheres to these ligands by means of specific adhesins. The presence of a foreign body decreases the minimal infecting dose of Staphylococcus aureus more than 100,000 fold.(33)

Biofilms can develop over weeks and years into organised and complex communities with structural and functional heterogeneity resembling multicellular organisms in which water channels serve as a rudimentary circulatory system in which nutrients can circulate between microbial cells.

Depletion of metabolic substances or waste product accumulation in biofilms causes microbes to enter a slow- or non-growing state. Release of cell-to-cell signalling molecules (quorum sensing) induced bacteria in a population to respond in concert by changing patterns of gene expression involved in biofilm differentiation. A subpopulation of the bacteria in the biofilm is named persisters. These microorganisms are up to 1,000 times more resistant to growth-dependent antimicrobial agents than their "free-living", planktonic counterparts and are more protected from host immune responses. And when the antibiotic concentration drops, the persisters resurrect the biofilm and there is relapse of infection (figure 1).(34–37)

Only a few antibiotics are able to kill off bacteria in biofilms with reasonable certainty, provided that the biofilm has had less than 3 weeks to develop. Rifampicin is able to eliminate staphylococci and streptococci, while quinolones are able to eliminate Gram-negative rods.

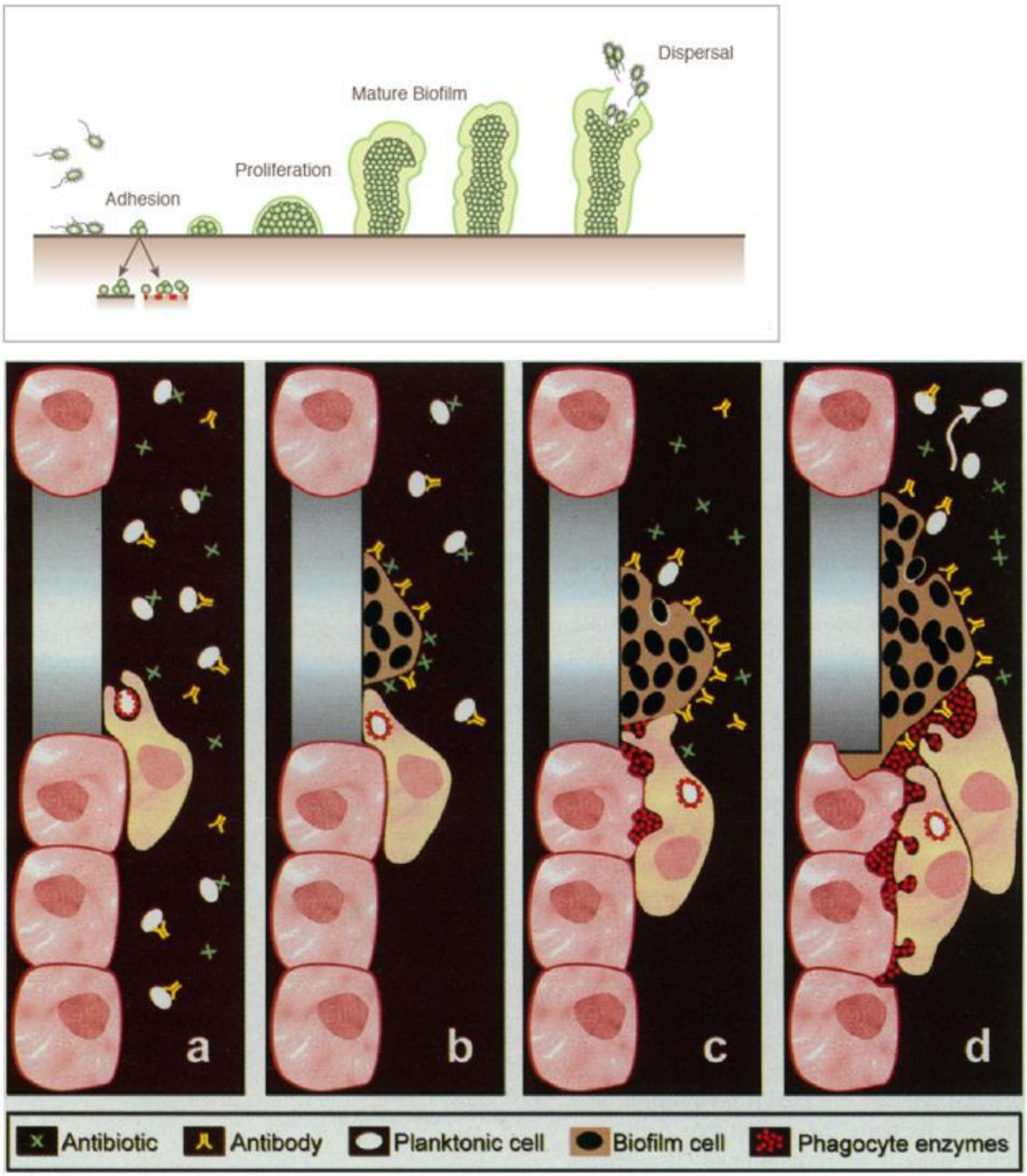

Figure 1. *Planktonic (free-floating) microorganisms forms a biofilm in which they are up to 1,000 times more resistant to growth-dependent antimicrobial agents than the planktonic form and are more protected from host immune responses. When the antibiotic concentration drops, the biofilm cells (persisters) resurrect the biofilm and there is relapse of infection.*

Microorganisms

Most common microorganisms that cause orthopaedic implant infections are Staphylococcus aureus and coagulase-negative staphylococci (CNS), of which Staphylococcus epidermidis in this context is the most important species. These microorganism are responsible for more than 50% of all orthopaedic implant infections. Mixed flora cause 10-11% of all deep infections, followed by streptococci (9-10%), Aerobic Gram-negative bacteria (3-6%), enterococci (3-6%) and anaerobic bacteria (2-4%).(38)

In instrumental spine infections Staphylococcus aureus is the most common cultured microorganism followed by coagulase-negative staphylococci. In contrast to instrumental spine infections coagulase-negative staphylococci (30-43%) cause most of the infections in total knee and hip prosthesis followed by Staphylococcus aureus (12-23%), only in the early postoperative prosthesis infections Staphylococcus aureus is more cultured than coagulase-negative staphylococci.(39–44)

Because the microbial diversity is so high, identifications and resistance testing is essential in the diagnosis of deep implant infection for adequate treatment.

Diagnosis

In clinical practice, the diagnosis of infection is made by sound interpretation of medical history, clinical signs, laboratory tests, diagnostic imaging, microbiology, and macroscopic findings during surgery.

A clear distinction has to be made between a superficial infection and an infection located within the joint capsule, involving the implant. An anatomy based nomenclature schema of nosocomial surgical site infections (SSIs) was presented by the Centers for Disease Control (CDC) in 1992.(45) This is now widely used for surveillance. According to this schema SSIs are divided into incisional SSIs and organ/space SSIs (involving the joint). In this work the organ/space SSI is termed as a deep infection. Although there is a protocol of the International Consensus Meeting in the making, at this moment no standardised criteria of infected implants are available.(26)

Clinical presentation

Clinical presentation of patients depend on the type of infection, the causing microorganism, and the immunological status of the patients. Clinical symptoms of an early or acute haematogenous infection include an acute onset of pain, effusion, erythema and warmth at the implant site. Fever is commonly caused by virulent microorganisms as Staphylococcus aureus and gram-negative bacilli. Excess wound exudate for a protracted postoperative period or renewed secondary secretion are suspicious for an early, acute infection. In acute haematogenous infection symptoms of a primary infection may be present.

Late (low-grade) infections usually present with subtle signs and symptoms, such as implant loosening, persistent joint/spinal pain and is difficult to distinguish from aseptic loosening (Figure 2). The causative microorganism are less virulent, such as coagulase-negative staphylococci and P. acnes.(26)

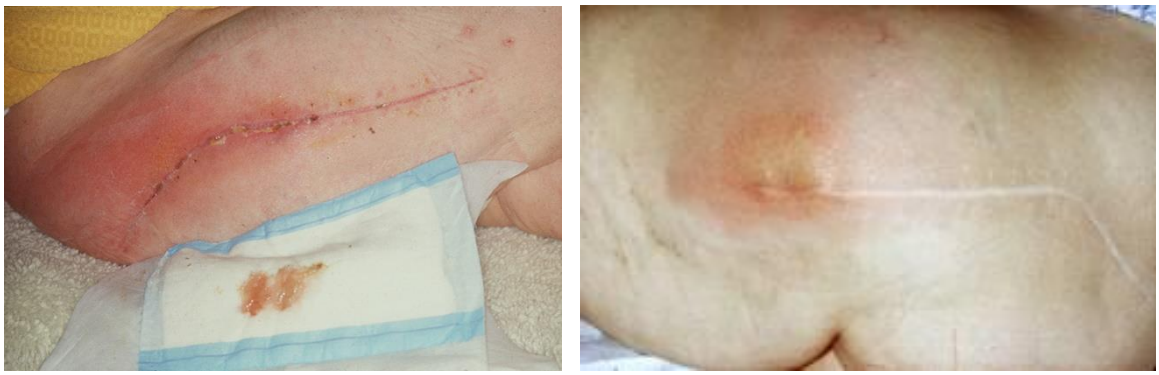

Figure 2. *Acute infection* *Chronic infection*

Culture

The reference standard for diagnosing infection of an orthopaedic implant is the isolation of responsible pathogens from intraoperative tissue samples from the peri-implant area. This provides the most accurate specimens for microbiological cultures, and is frequently used as the standard method in diagnosing infection after an orthopaedic implant. The sensitivity of these cultures ranges from 65-94%, as different cut-off values are used in several studies.(39) Shortcomings of this method are the diagnostic delay and sensitivity of cultures. Some cultures are easily grown in three days, but especially culturing of anaerobic and slowly growing biofilm organisms can take more than 2 weeks. The formation of small colony variants may limit the ability of the laboratory to isolate the microorganism. New rapid molecular methods, like IS-pro, may alleviate these obstacles.(46) Also, not infrequently, previous or simultaneous antibiotic treatment in patients with an orthopaedic implant may lead to false negative test results and should be discontinued at least two weeks before tissue specimens are obtained. In revision surgery, perioperative prophylaxis should not be administered until after tissue specimens have been collected for cultures. At least three intraoperative tissue specimen should be sampled for culture. Sensitivity increases from 50% with 2-3 samples to 72.7% with more than 5 samples. More samples reduce the risk of an incorrect assessment due to contamination.(47) Swab cultures have a low sensitivity and should be avoided. Biofilm bacteria cannot be extracted from biofilms using swabs and swabs may contain microbial contamination. Cultures of a superficial wound or sinus tract are often positive because of microbial colonization from surrounding skin and should also be avoided. Aspirated synovial fluid can be helpful in the work up for infection with a detection rate of the pathogen between 45-100%.(39)

Sonication is used to identify the bacteria in the biofilm on explanted implants. The implants vortexing in a liquid bath where ultrasonic waves generate a rapid change in pressure on the surface of the implant which dislodges the biofilm. The liquid is then used to diagnose bacterial infection with conventional culture (figure 3). Sonication increases the sensitivity for detecting the causing microorganism compared to tissue biopsy from 60.8% to 78.5% with identical high specificity.(48,49)

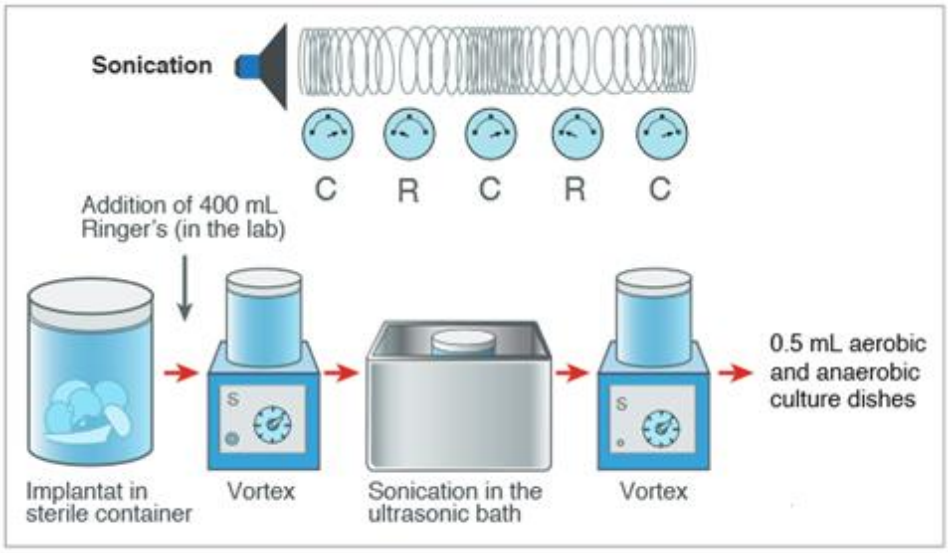

Figure 3. *Diagram of sonication workflow. Ultrasonic penetration takes place through alternating phases of compression (C) and rarefaction (R).*

Laboratory

There is no blood test that can unequivocally detect the presence of an infection. For CRP the level is independent of age, sex, blood loss and anaesthesia. The extent of the surgical procedure, the administration of steroids or other immunosuppressive medication and/or postoperative haematoma influence the CRP level. It increases within 6–24 hours in response to inflammatory processes and has a half-life of approximately one day. As a result, the CRP level is an important postoperative clinical parameter. It usually peaks on postoperative day 2–3 and then continues to fall steadily over a postoperative course free of complications. A persistently elevated CRP level or a postoperative increase may indicate an infection at the site of the operation. The sensitivity and specificity values reported in the case of periprosthetic hip and knee joint infections are: sensitivity 91–96%, specificity 74–92%.(26)

Because an elevated white blood cell count can have a number of causes, the sensitivity for implant infection is only 75% and the specificity only 55%.

ESR is non-specific with a low diagnostic specificity. For periprosthetic infections the sensitivity is 82-93% and the specificity is 66-85% and therefore not recommended for diagnostics.(50)

Diagnostic imaging

Imaging diagnostics for infections in implant includes a conventional x-ray as the first imaging procedure for signs of loosening, radiolucent lines. Serial x-rays over a certain period can measure changes to the cortical bone (new sub periosteal bone growth and transcortical sinus tracts) and migration of an implant. Rapidly progressive or irregular periprosthetic osteolysis suggests an infection (figure 4).(51)

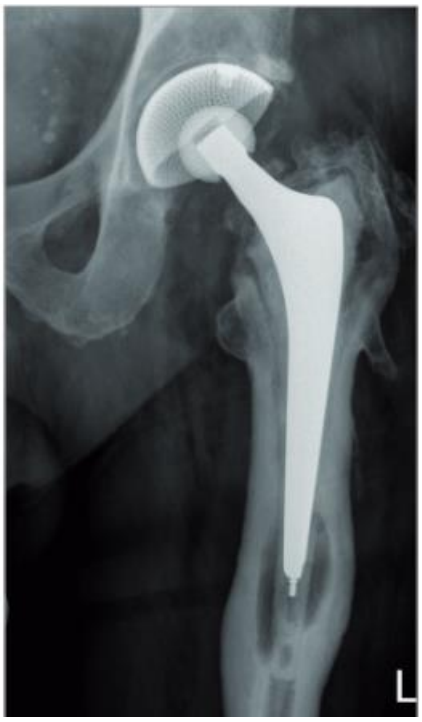

Figure 4. *Chronic infection of a total hip prosthesis with periprosthetic osteolysis and subperiosteal bone growth.*

Small changes are often less specific for infections. For sequestra, fistulas or abscesses other imaging techniques like MRI and CT are more reliable. Contrast-enhanced arthrography is especially useful in hip prosthesis, it reveals protrusions from the joint cavity, abscess cavities, and fistulous tracts, even without external fistula.(33,52)

Ultrasound examination can be useful for controlled puncture and drainage of effusion.
In case of suspected low-grade infections or complex situations, further imaging with SPECT/CT with scintigraphy or FDG-PET/CT must be considered (figure 5). Scintigraphic scans (^{99m}Tc, ^{99m}Tc-labelled monoclonal antibodies) show the physiological processes that precede radiologically visible, anatomical changes. With SPECT/CT these processes can be localised and increase the specificity of the scans, without the need for additional CT or MRI. Bone scintigraphy has an excellent sensitivity, but a low specificity for diagnosing implant infection. In addition, increased bone remodelling around the prosthesis is normally present during the first post-operative years and aseptic loosening cannot be differentiated from infection.(53–56)

FDG-PET/CT is a highly sensitive imaging modality for chronic infections that colours regional glucose metabolism by phagocytes. In literature the reliability for differentiating between an infection and aseptic loosening is still considered controversial because of the lack of standardised interpretation criteria.(57,58)

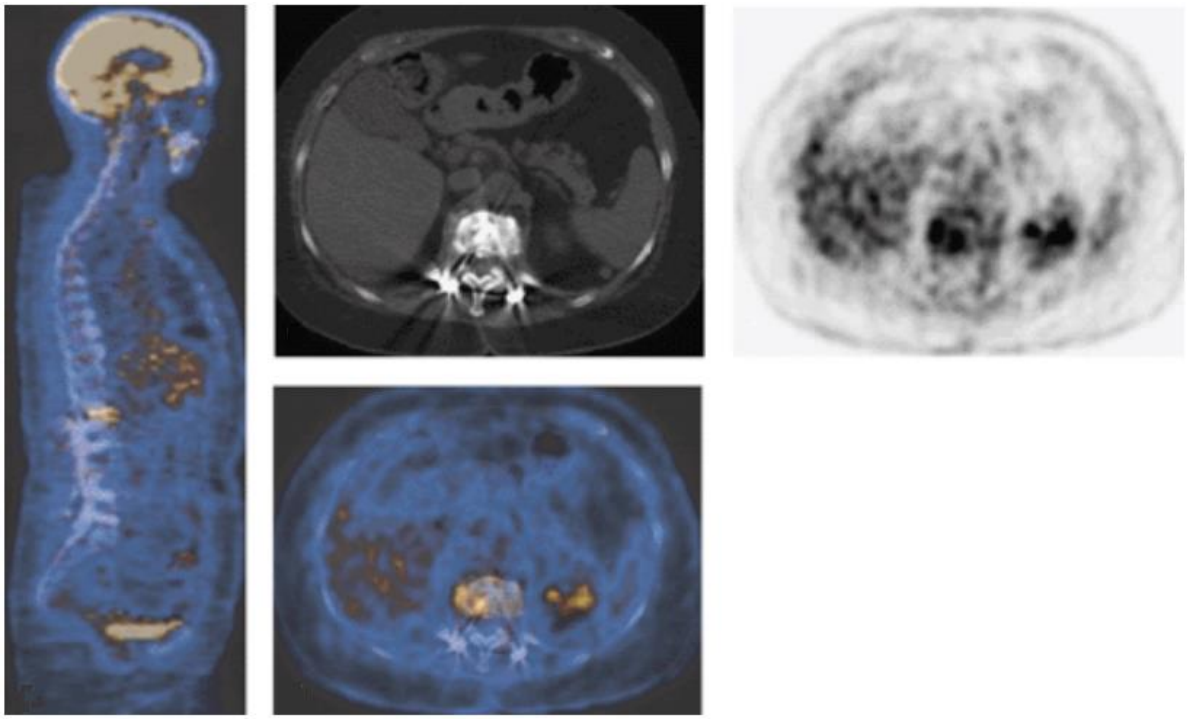

Figure 5. *PET/CT of low grade infection 2 years after decompression and instrumented spondylodesis of L1/L2. There is an increased FDG uptake in the region of the right cranial screw in the L1 vertebral body corresponding to osseous infection.*

Incidence and consequences

Despite the large number of operations performed each year, it is difficult to obtain reliable information on the true incidence of infection. The national registries provide some information, but are not qualified/reliable because of methodological differences with different endpoints between registries. An important weakness of national arthroplasty registers is that they are not designed for registration of infections and postoperative infections are underestimated. In most registers the surgeon register immediately after the operation whether or not revision/reoperation is due to an infection, based on a subjective assessment, without knowing the outcome of preoperatively taken biopsies.(19) Even a minimal postoperative infection rate of 0.5-2% will constitute a major concern, considering the financial burden that is more than twice as much for cases with a SSI compared to patients without SSI.(59,60)

Postoperative infections lead to an increase of spinal non-union, osteomyelitis, implant loosening, sepsis, multiorgan dysfunction and even death. The length of the hospital stay may increase with 5.8 to 17 days. Patients with surgical site infections (SSI) also utilizemore healthcare resources, including outpatient and emergency department visits, radiology, and home health aides. They were also readmitted more frequently. The costs of revision procedures caused by infection will increase in future and treatment is becoming more complex because of more complicated infections by the emergence of new resistant bacterial strains as well as infections with rare organisms.(61–63)
In the Netherlands there is lack of high quality cost analysis of prosthetic infection. In the US the combined annual hospital costs related to prosthetic joint infection (PJI) of the hip and knee were estimated to be $1.85 billion by 2030. This includes $753.4 million for THA PJI and $1.1 billion for TKA PJI.(61, 64)

SSI after instrumented spinal surgery is also associated with higher rates of morbidity and mortality, which leads to prolonged treatment with the need for subsequent reoperations and substantially increased overall health care costs.(65)
The average total cost for spinal surgery experiencing postoperative deep SSI was $37,009 compared to $16,227 for patients not experiencing a deep SSI. These costs were higher for hospitalizations ($p < 0.01$), office visits ($p = 0.03$), imaging ($p < 0.01$), and medications ($p < 0.01$).(59)

Surprisingly little information is available on the effect of infected implants on quality of life. When compared with patients with uncomplicated joint arthroplasty, patients with infection scored significantly lower in satisfaction scales. (66) Also patients with SSI after spine surgery have substantially greater physical limitations and a distinct decrease in quality of life.(60,67)

Risk factors and predictive models

Risk factors, associated with surgical site infection in orthopaedic implants can be divided into patient related risk factors that limit a patient's ability to eliminate intra-articular microorganisms, and factors that increase the risk of exposure of operation area to microorganisms. Patient related risk factors are comorbidities, malnourishment, immunosuppressive drugs and vascular insufficiency. Risk factors that increase the risk of exposure include inadequate sterilization, lamellar air flow, cold operation theatres, casual mood of surgeons, inadequate scrubbing, more movements into operation theatre, long duration of surgeries, and inadequate postoperative wound management with prolonged wound leakage.(26)

Perioperative infections are primarily triggered by the patient's skin flora and may also be caused by bacteria present in the surrounding ambient air. Many such infections are preventable. Perioperative infections occur peri- or postoperatively.
Preoperative risk factors must be reduced to a minimum. Blood glucose levels should be kept under optimal control in patients with diabetes and smoking must be advised to stop/reduce to minimum. Nutrition status and general condition of the patient must be optimised before surgery. Patients with systemic or local bacterial infections must be treated accordingly before elective surgery should be postponed. Only asymptomatic colonisation of the urinary tract does not need treatment.(68,69)
Predictive models are appropriate tools to use pre-operative to calculate the relative risk for a surgical site infection by combining several risk factors for the individual patient. This relative risk can be useful for shared decision making during work up for an orthopaedic procedure.

Treatment

The primary objective of treatment are the elimination of infection and a correctly functioning implant.

In the last decades the treatment of infected implants has changed worldwide gradually. In the sixties and seventies the common therapy of osteomyelitis or prostheses infections after debridement was suction-irrigation for 4-6 weeks.(70,71)

The admixture of antibiotics to commercial poly methyl methacrylate (PMMA) bone cement was invented by Hans Wilhelm Buchholz. He developed his concept in collaboration with the German companies Merck and Kulzer, starting in 1969.(72)

The use of PMMA as a drug carrier with sustained release of gentamicin proved to be a perfect combination. This combination was a successful indication for prophylactic use in primary prosthesis implantation and proved a preventive effect on deep postoperative infections and loosening probably due to non-diagnosed low grade infections.

The therapeutic properties of PMMA as an antibiotic delivery system were improved by the development of PMMA beads: more porous cement, an increased amount of gentamicin and above all the increase in the total releasing surface resulted in a potent local antibiotic instrument.

The development of gentamicin PMMA beads in the 1976 was the better alternative for suction-irrigation systems, made it possible to close primarily the wound, administration of antibiotics in the joint, and to mobilise the patient. The main advantage was a local high antibiotic delivery without systemic toxicity (figure 6).(7)

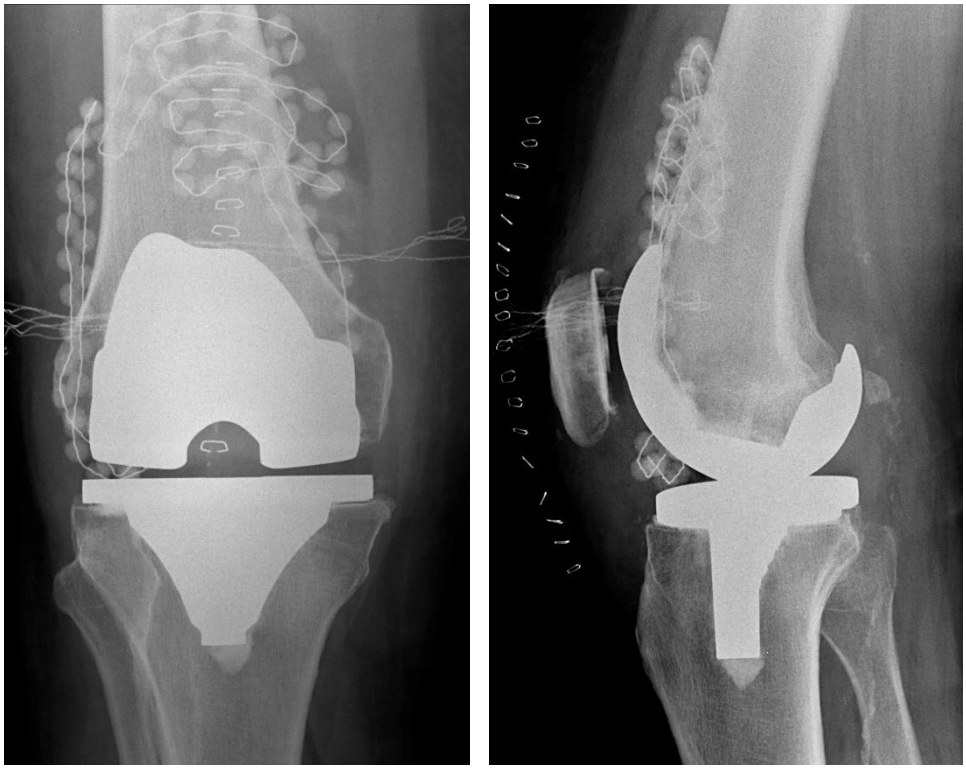

Figure 6. *Infected TKP with PMMA beads in situ*

The introduction of spacers, initially hand-modelled and pre-modelled and later custom-made, improved the technical possibilities for the two stage approach (figure 7).(74–77)

Figure 7. *Hip and knee spacers*

Spacers facilitate largely the reimplantation, because of maintaining length, reducing the risk of dislocation and facilitate non-weight bearing mobility. They allow for greater patient comfort during intervening period between removal and reimplantation. Disadvantage of spacers is an inferior release of antibiotics, when compared with beads, due to a largely reduced surface and as another composition of the gentamicin loaded carrier. Despite this inferior antibiotic elution in spacers, there is no evidence that infection treatment with antibiotic loaded spacers results in more persistent infection then treatment with antibiotic loaded PMMA beads.(75,78–81)

Nowadays there are six different types of intervention for an implant infection.
Depending on the type of infection, the causative bacteria, the comorbidities of the patient and the soft tissue condition.

- In acute infections with a short duration of symptoms, a stable implant, sufficient soft tissue, susceptible causative microorganism and operable patient the implant can be retained with an extensive debridement of the implant and peri implant tissue. This procedure can be combined with local antibiotics (antibiotic loaded PMMA beads or collagen).(82,83)
- In late infections with symptoms that longer exist or a non-stable implant the implant must be removed. If the causative bacteria is susceptible for antibiotic treatment and the soft tissue is sufficient it is possible to do an one-stage reimplantation with extensive debridement with or without local antibiotics. Removing the implants means removing of all foreign bodies including cement and grafts. Also in cases where an implant is necessary because of the need for stability (e.g. spinal implants) an one stage reimplantation is the appropriate treatment. If cement is used for the reimplantation it is recommended to use antibiotic loaded cement. Systemic antibiotics depending on the resistant pattern of the causative microorganism should be administered for a prolonged period after reimplantation.(84,85)
- In late infections with longer duration of symptoms where the implant can be removed temporarily (prosthetic joint infection) and insufficient soft tissue or difficult to treat causative microorganisms (e.g. multi-resistant microorganisms) a two-stage reimplantation is recommended. In the first procedure the implant is removed

with extensive debridement of the peri implant tissue and mostly local antibiotics (antibiotic loaded spacer or antibiotic loaded PMMA beads) left behind. During the period between removal and reimplantation the patient is monitored for elimination of infection and soft tissue recovery at which sometimes a second or third procedure with debridement and local antibiotics is necessary. The period between removal of the implant and reimplantation can be a short interval for recovery of the soft tissue or a long interval to treat the infection till enough evidence for elimination of the infection. This can be done by an aspiration after a period without antibiotics. If the patient is free of infection symptoms and soft tissue is sufficient the last procedure includes a reimplantation.(86,87)

- In some cases of implant infection the implant is removed without a reimplantation. This is possible when implants are not that necessary (e.g. stable spine or fracture site after removing implants). In cases with prolonged medical history with various unsuccessful attempts at therapy or severely damaged soft tissue the implant can be removed without reimplantation (hip or shoulder joint) or removing of the implant followed by an arthrodesis (knee, ankle, wrist).(88)
- Amputation can be done in severe damaged bone and soft tissue or when sepsis cannot be controlled.
- In patients who are not operable because of poor general condition, anaesthesia involves high risks or patient is not willing to undergo an operation, suppressive long-term therapy with antibiotics is the only treatment left.(82)

Aim of this thesis

Aim 1

What are the results of operative debridement with retention of the prosthesis and local antibiotics after postoperative and haematogenous deep infections of stable total hip and knee replacements?

In the second chapter the treatment of a cohort of 89 postoperative and haematogenous deep infections of stable total hip and knee replacements with retention of the prosthesis and local antibiotics is studied. We evaluate the influence of the postoperative interval since implantation and the duration of symptoms on the success rate of the infection treatment with retention of the prosthesis.

Aim 2

What are the results of a two-stage infection treatment and local antibiotics in infected total knee and hip prosthesis?

The third chapter of this thesis describes a study that evaluate the outcome regarding infection healing and clinical results of a two-stage revision treatment with help of local antibiotics in 120 deep infected total hip and knee prosthesis. All infections were treated with extraction of the prosthesis, 1 or more debridements with systemic and local antibiotics in the form of gentamicin-PMMA beads, and reimplantation of the prosthesis. Different intervals between extraction and reimplantation were used.

Aim 3

What are the results of a treatment protocol including local antibiotics in surgical site infections after instrumented spine surgery?

The study described in the fourth chapter of this thesis evaluates 48 non-union deep SSI after instrumented spine surgery treated with a treatment protocol consisting of repetitive surgical debridement, supplemented with local gentamicin releasing carriers and systemic antibiotics, between 1999 and 2016. The intention of this treatment protocol was to retain the instrumentation or eventual restabilize the instrumentation during surgical debridement in case of loosening to keep a stable spine. The evaluation of the treatment protocol is described in eradication of the infection and residual pain or limitations in daily living.

Aim 4

How performs a previously published prediction model for surgical site infection after spine surgery in an independent patient cohort?

In the fifth chapter of this the thesis the external validation of a previously published prediction model for surgical site infection after spine surgery is studied. The previously published prediction model was derived from a surgical spine register of the United States to compute an individual risk for SSI after spine surgery. To analyse the general applicability of this model we externally validated the prediction model in an independent Western European cohort who received instrumented spine surgery.

Aim 5

How to use several risk factors in daily practice to estimate the risk of SSI after instrumented spine surgery for an individual patient?

The sixth chapter describes the development and internally validation of a multivariable prediction model for surgical site infection after instrumented spine surgery. For this development we used a large cohort of a Western European academic center. Combining several risk factors into this new prediction model is an appropriate tool in daily practice for preoperative patient counselling to evaluate the individual risk of SSI after instrumented spinal surgery. Optimizing patient selection by estimating an individual risk and identify high risk patients can possiblyprevent devastating consequences of an SSI after surgery.

Aim 6

What is the elution profile of several local antibiotics used in orthopaedic infection treatment?

The seventh chapter of this thesis focuses on the elution of antibiotics in different local antibiotics used in the treatment of orthopaedic surgical site infections. We described the elution of antibiotics from PMMA beads and spacers during time.

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Good results in postoperative and hematogenous deep infections of 89 stable total hip and knee

J Geurts
DMC Janssen
AG Kessels
GHIM Walenkamp

Acta Orthopedica 2013

Chapter II

Good results in postoperative and hematogenous deep infections of 89 stable total hip and knee replacements with retention of prosthesis and local antibiotics

Jan A P Geurts, Daniël M C Janssen, Alfons G H Kessels, and Geert H I M Walenkamp
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Abstract

Background. Deep postoperative and hematogenous prosthesis infections may be treated with retention of the prosthesis, if the prosthesis is stable. How long the infection may be present to preclude a good result is unclear.

Patients and methods. We retrospectively studied 89 deep infected stable prostheses from 69 total hip replacements and 20 total knee replacements. There were 83 early or delayed postoperative infections and 6 hematogenous. In the postoperative infections, treatment had started 12 days to 2 years after implantation. In the hematogenous infections, symptoms had been present for 6 to 9 days. The patients had been treated with debridement, prosthesis retention, systemic antibiotics, and local antibiotics: gentamicin-PMMA beads or gentamicin collagen fleeces. The minimum follow-up time was 1.5 years. We investigated how the result of the treatment had been influenced by the length of the period the infection was present, and by other variables such as host characteristics, infection stage, and type of bacteria.

Results. In postoperative infections, the risk of failure increased with a longer postoperative interval: from 0.2 (95% CI: 0.1–0.3) if the treatment had started ≤4 weeks postoperatively to 0.5 (CI: 0.2–0.8) if it had started at ≥ 8 weeks. The relative risk for success was 0.6 (CI: 0.3–0.95) if the treatment had started ≥8 weeks. In the hematogenous group, 5 of 6 infections had been treated successfully.

Interpretation. A longer delay before the start of the treatment caused an increased failure rate, but this must be weighed against the advantage of keeping the prosthesis. We consider a failure rate of < 50% to be acceptable, and we therefore advocate keeping the prosthesis for up to 8 weeks postoperatively, and in hematogenous infections with a short duration of symptoms.

Introduction

The incidence of deep infection in total hip and knee replacement (THR, TKR) ranges from 1% or less in primary THR and TKR to 5% in revision settings and even up to 21% when revising for infection.(1-3) Early deep prosthesis infections are probably caused by perioperative contamination, and in the literature there is agreement that if the prosthesis is stable such an early infection can be treated without removal of the prosthesis, as in early postoperatively infected osteosynthesis.(4-6) The same holds true for hematogenous prosthesis infections.(5) However, for postoperative infections there is no agreement about the maximal period between implantation of the prosthesis and the start of the treatment that permits retention of the prosthesis, or the duration of symptoms in acute onset of hematogenous infections.(7,8)

At our institution, deep postoperative or hematogenous infections of THR and TKR are treated with retention of the prosthesis if they are stable, regardless of interval period since implantation or duration of symptoms. We investigated whether this policy was justified and questioned whether the success rate in postoperative infections does indeed decrease when the postoperative interval since implantation increases or the duration of symptoms in hematogenous infections increases.

Patients and methods

We performed a retrospective cohort analysis of a prospective register of all proven early and delayed deep infections of THR and TKR with a postoperative interval after prosthesis implantation of less than 2 years, and all hematogenous infections treated at our center from January 1982 to July 2010. As hematogenous infections, we considered delayed or late deep infections without any sign of prosthesis infection in the period since implantation.

Table 1. *Data on the infected prostheses (69 THRs and 20 TKRs) scored according to the different staging of the host and wound, and classification of the infection. The numbers of THRs and TKRs are given for each subclass, as are the results of the treatments*

Staging or classification	Subclasses	THR total 69	THR success 57	THR failure 12	TKR total 20	TKR success 17	TKR failure 3
ASAscore patient	ASA1	9	8	1	4	4	0
	ASA2	36	30	6	10	9	1
	ASA3	24	19	5	6	4	2
McPherson classification of infection	type I early postop (< 4 weeks)	42	37	5	8	8	0
	type II hematogenous	3	2	1	3	3	0
	type III late postop (> 4weeks)	24	18	6	9	6	3
McPherson host staging	host A: uncompromised	22	19	3	7	7	0
	host B: compromised	38	32	6	13	10	3
	host C: significant compromised	9	6	3	0	0	0
McPherson wound staging	grade 1: uncompromised	17	15	2	9	9	0
	grade 2: compromised	43	37	6	10	8	2
	grade 3: significant compromised	9	5	4	1	0	1
Cierny host staging	A-host: uncompromised	7	6	1	5	5	0
	B-host: compromised	62	51	11	15	12	3
	C-host: significant compromised	0	0	0	0	0	0
Zimmerli classification of infection	early postop (< 3 months)	61	53	8	14	12	2
	acute hematogenous	3	2	1	3	3	0
	delayed exogenous (3–24 months)	5	2	3	3	2	1
This study: classification of infection	postop infection < 8 weeks	60	53	7	9	9	0
	postop infection ≥ 8 weeks	6	2	4	8	5	3
	hematogenous	3	2	1	3	3	0

In the databases of the hospital and department, we found 145 infections in 144 patients. For this retrospective analysis, we studied the medical records and if necessary we contacted the patient or family doctor.

Prostheses were diagnosed as infected when the Mayo criteria were fulfilled: growth of the same microorganism in 2 or more cultures of synovial fluid or periprosthetic tissue, or pus in synovial fluid or at the implant site, or histological examination showing acute inflammation in periprosthetic tissue, or a sinus tract communicating with the prosthesis.(9)

We excluded the following patients. 16 patients did not meet Mayo criteria for deep infection, 21 patients got their first surgical treatment at another center, 12 patients were treated by immediate extraction of the prosthesis since unexpected loosening was diagnosed during operation, and 2 patients were excluded because of incomplete patient files. Also excluded were 5 patients with TKR who did not receive any local antibiotic treatment, but only arthroscopic debridement.

After these exclusions, 89 deep infections remained (88 patients, 46 women). All patients and types of infections were scored according to classifications of ASA, Cierny, McPherson, and Zimmerli (Table 1).(7, 10) There were 69 THR infections (39 primary THR, 30 revisions) and 20 TKR infections (19 primary TKR, 1 revision). 3 of the THR infections and 3 of the TKR infections were hematogenous. One female patient had an early postoperative infection in a primary TKR on both sides, not simultaneously. The first TKR infection was successfully treated, but the contralateral TKR that was subsequently implanted was also infected.

The median age of the patients at the start of the infection treatment was 69 (27–93) years. The median interval between implantation of the prosthesis and the first operation for infection in the postoperative THR infections was 23 (12–390) days, and in the TKR infections the median interval was 42 (14–713) days. In some cases, the delay was caused by a period of intravenous antibiotic treatment of a supposed superficial postoperative infection. In 3 hematogenous THR infections, the median duration of symptoms was 7 (6–9) days before the debridement for infection, and in 3 hematogenous TKR infections it was 8 (6-9) days.

No loosening was suspected in any of the implants preoperatively, and this was confirmed peroperatively.
The treatment consisted of arthrotomy, debridement (including pulse lavage with at least 3 L of Ringer lactate), and retention of the implant. In the period studied, we did not exchange modular components if present. The patients were treated with systemic antibiotic therapy, and also with local antibiotic carriers. We preferred the use of gentamicin-PMMA beads with a size of 7 mm, containing 7.5 mg gentamicin sulfate, in the form of chains with 30 or 60 beads (Septopal; Merck GmbH, Darmstadt, Germany; Biomet GmbH, Berlin, Germany). We implanted as much beads as possible in the infected tissues to create a high local gentamicin concentration (Figures 1–3).

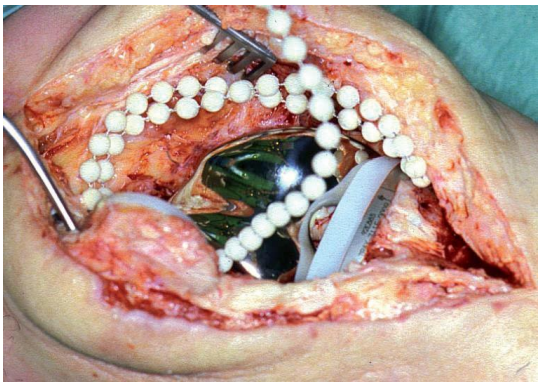

Figure 1. *Gentamicin-PMMA beads (Septopal) inserted in a total knee replacement after debridement with retained prosthesis. Beads are mainly placed in the suprapatellar bursa and are removed after 2 weeks by another operation under general anesthesia, but with a smaller incision.*

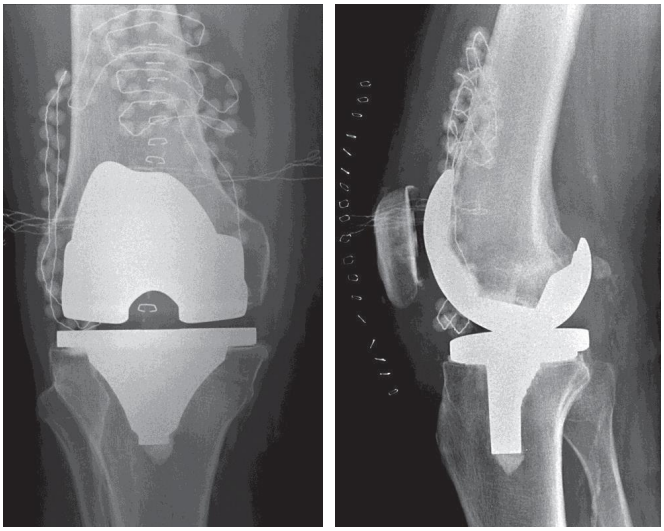

Figure 2. *Radiographic appearance of a TKR in 2 directions. Gentamicin-PMMA beads are visible in the suprapatellar bursa and on the lateral side of the joint. Beads cannot be positioned in the posterior joint due to the limited space.*

Beads did not stick through the skin, but were removed in a second operation after 2 weeks. This operation consisted of a new debridement, leaving behind new beads if infection was not considered to be eradicated. If healing was considered appropriate, a much smaller incision was sufficient for the removal of the beads. In several infections, the surgeon implanted gentamicin collagen fleeces (Septocoll containing 116 mg gentamicin sulfate and 350 mg gentamicin crobephate in 320 mg equine collagen fleece with a size of 10 × 8 cm; Merck GmbH; Biomet GmbH) in the joint during the last operation before closing the wound, to increase the period with local antibiotics. If the infection persisted, according to clinical and laboratory parameters and despite one or more treatment periods of 2 weeks with beads, the prosthesis was removed and the treatment for infection continued with gentamicin-PMMA beads.

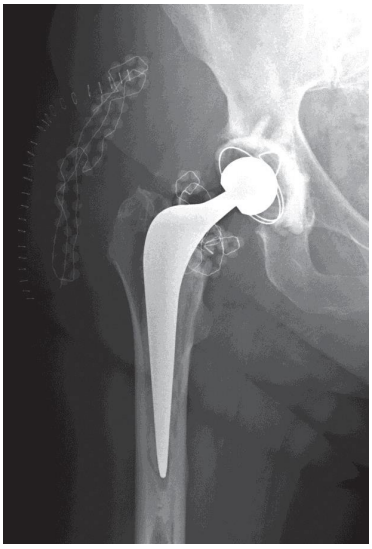

Figure 3. *THR with gentamicin-PMMA beads intra-articularly around the neck of the prosthesis and in the subcutaneous tissues. Antero-posterior radiograph on the first day after the debridement operation. Only a limited number of beads could be placed in this joint after the debridement. In the subcutaneous tissue, beads were placed in an abscess cavity.*

Of the infected THRs, 26 of 69 were treated in a single period of 2 weeks with beads or fleeces, and 47 of the 69 THR infections required 2 or more debridements with a subsequent period of 2 weeks of local antibiotics (Table 2). The THR infections were treated with implantation of an average of 180 (30–420) gentamicin beads. Of the infected TKRs, 13 of 20 patients were given a single treatment of 2 weeks of local antibiotics and 7 TKR infections needed 2 or more debridements with local antibiotics for 2 weeks. In 15 of the 20 TKR infections, we implanted an average of 120 (50–240) beads. In the remaining 5 TKR infections, no beads but only gentamicin fleeces were inserted due to limited joint size (Table 2). In the 84 patients who were treated with gentamicin beads, these were removed at the last surgery by a limited operation with a small incision. In 22 of these 84 infections, we implanted 1–4 gentamicin collagen fleeces at this last removal operation of the beads.

Swabs as well as multiple tissue cultures were taken. The samples were cultured in the microbiology laboratory for at least 2 weeks to detect slow-growing microorganisms, and minimal inhibitory concentrations (MICs) of gentamicin for the bacteria were determined.

Table 2. *Numbers of debridements and local antibiotic carriers in 89 THR and TKR infections. Detailed numbers are given to specify whether beads were used with or without fleeces (at the last operation), or only fleeces, with numbers of successful or failed treatments*

	No of prostheses	No of debride-ments	Beads ± fleeces	Only fleeces	Success	Failure
THP						
	26	1	26	0	24	2
	32	2	32	0	27	5
	8	3	8	0	6	2
	3	4	3	0	0	3
Total	69		69	0	57	12
TKR						
	13	1	11	2	12	1
	4	2	2	2	3	1
	3	3	2	1	2	1
Total	20		15	5	17	3

We found methicillin-sensitive *Staphylococcus aureus* to be the most frequent microorganism to cause infections (31/89) (Table 3). In 2 patients, peroperative cultures showed no growth, due to systemic use of antibiotics preoperatively. In the 27 polymicrobial infections, we found 68 bacterial species in many combinations, with *Pseudomonas aeruginosa* and *Enterobacter spp.* being the most frequent (Table 4).

The MIC values for gentamicin of the causative bacteria were ≤8 µg/mL in 71 infections, 16–64 µg/mL in 11 infections, and ≥128 µg/mL in 5 infections.

The surgical treatment was combined with high doses of systemic antibiotics, intravenously during hospitalization and continued orally after discharge from hospital. The choice of the antibiotic was based on the resistance pattern of the deep tissue cultures and on consultation with a microbiologist with an interest in orthopedic infections. From 2004, we added rifampicin in the systemic antibiotic treatment of infected implants routinely: thus, 25 of the THR infections and 7 of the TKR infections were also treated with rifampicin. The antibiotic treatment was given for a period of 30 (10–82) days intravenously, followed by an oral treatment over 72 (7–1,310) days. The median total antibiotic therapy time was 95 (12– 1,310) days. We stopped the oral antibiotic treatment at the outpatient clinic when clinical and laboratory parameters had normalized for at least 4 weeks.

As laboratory parameters for infection we used ESR, CRP, and WBC counts. These were measured twice a week during hospitalization, and at all the outpatient control visits. We considered these parameters to be normalized when at 2 subsequent controls CRP and WBC counts remained normal, and when the ESR was reduced to less than 30 mm/h in patients with no systemic diseases.

The treatment was considered to be successful when the infection was resolved at follow-up (normalized inflammatory blood markers and no clinical or radiological signs of recurrence) with retention of the prosthesis.

Table 3. *Causative bacteria in 89 prosthesis infections*

Causative microorganism	THR	TKR	%
Staphylococcus aurues	26	5	35
MRSA	1	0	1
CNS	1	5	7
Streptococcus spp.	6	2	9
Enterococcus spp.	1	0	1
Enterobacter spp.	5	1	7
Pseudomonas aeruginosa	4	1	56
Cutibacterium acnes	1	1	2
Polymicrobial	24	3	30
Negative culture	0	2	2
Total	69	20	100

Table 4. Bacteria present in the 27 polymicrobial infections as depicted in Table 3

Microorganisms in polymicrobial culture	THR	TKR
Staphylococcus aurues	14	3
CNS	4	0
Streptococcus spp.	4	1
Enterococcus spp.	18	0
Enterobacter spp.	2	0
Pseudomonas aeruginosa	15	1
Cutibacterium acnes	5	0
Prevotella	0	1
Total microorganisms	62	6
Number of infections	24	3

Failure was diagnosed if the patient never became infection-free or if removal of the implant was necessary for healing of the infection. The follow-up period started at the first operation for deep infection, and the end of the follow-up period was either the date of the last outpatient clinic visit, the last contact with the family doctor, or the date of death. The minimum follow-up was 1.5 years, but possibly shorter if patients died before—whether or not this was related to the infection. Mean follow-up time was 33 (1–270) months for all infections, 27 (1–270) months for infected THRs, and 52 (3–202) months for infected TKRs. In the group of postoperative infections, we analyzed how the treatment result was influenced by the length of the interval between implantation of the prosthesis and the start of the treatment. In the hematogenous infections, we studied the influence of the duration of symptoms before the treatment started. We also studied the influence on the result of staging of host and of the wound, of classification of patients, of infection parameters at the start of the treatment, of the causative bacterial species, and of the MIC of gentamicin for the Bacteria.

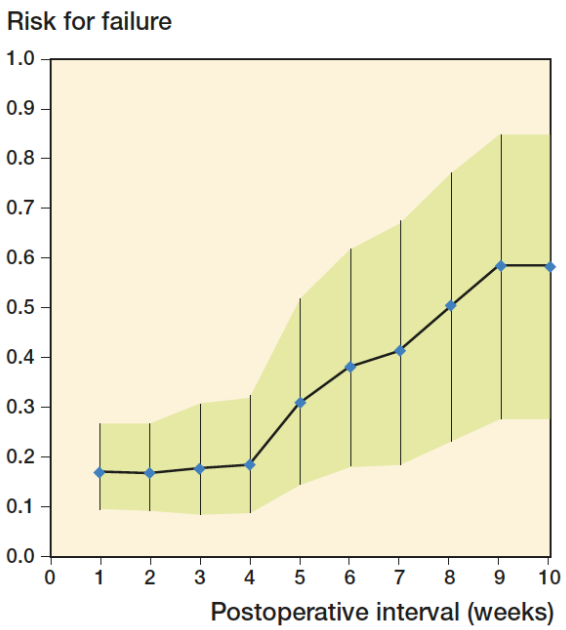

Figure 4. *Risk (with 95% CI) for failure of the treatment of an infected prosthesis if treated at or after a particular postoperative time interval.*

Statistics

Data are presented as median (total range) or as mean (SD). We analyzed the relationship between the result and the length of the postoperative interval using the following steps. For each of the first 10 postoperative weeks, we distinguished 2 periods: the period including and after (≥) a particular week, and the period before (<) that particular week. For both periods, we then estimated the number of failures and successes. Then we estimated first the risk of failure at or after that week. Secondly, we determined the relative risk (RR) with 95% confidence intervals (CIs) for success comparing the results in the period at or after that week with the results obtained before that week. For these calculations, we used Stata 11 for Windows.

Using SPSS version 17.0 for Windows, we calculated RR with CI to determine the influence of the host and wound staging on the result of the treatment. We tested differences between proportions with chi-square test or Fisher's exact test. We used the Mann-Whitney U test to examine the influence of preoperative body temperature, laboratory values, and the MIC of gentamicin for the causative bacteria on the result of the treatment.

Results

Of the 89 infected prostheses, 74 infections were treated successfully with retention and 15 treatments failed. In the group of postoperative infections, 55 of 66 THRs were treated successfully, and 11 treatments failed. 10 of these 11 prostheses were removed at a later stage. In TKR patients, 14 of 17 prostheses were successfully treated. In 3 TKRs there was no successful eradication of infection, resulting in removal of the implant in 2 patients. 2 of the 3 hematogenous THR infections were treated successfully, and 1 failed but became infection-free after extraction of the implant. 3 of 3 hematogenous TKR infections were successfully treated with retention of the implant.

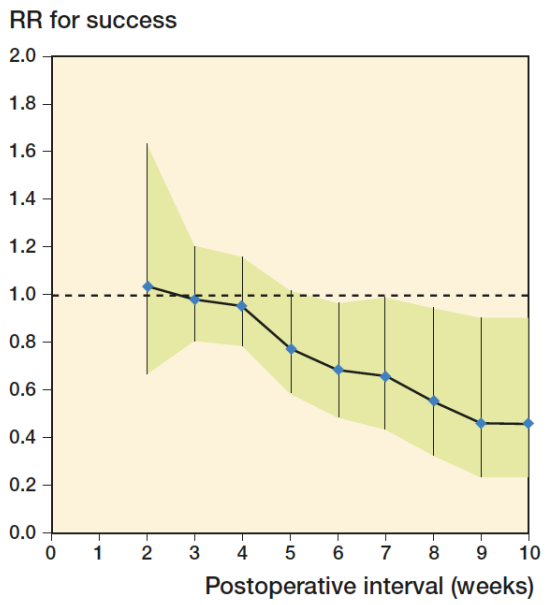

Figure 5. *Relation between the relative risk (RR) for successful treatment of an infected prosthesis and the postoperative interval in weeks. The RR is expressed as success if a treatment started after ≥ N weeks, as compared to the period < N weeks. The null hypothesis of RR = 1.0 is represented by a broken line.*

4 patients died during the course of treatment, either because of sepsis or poor health: 3 with THR (at 1, 3, and 8 months after the start of treatment), and 1 with TKR (at 8 months). 8 other patients died of other causes 6–17 months after the treatment started; none of them had signs of infection, so they had probably resolved. In the first 4 weeks postoperatively, the risk of failed treatment remained almost unchanged and gradually increased thereafter, week by week. The risk of failure in the group of patients where the treatment started ≤4 weeks was 0.2 (CI: 0.1–0.3), and it was 0.5 (CI: 0.2–0.8) when the treatment started ≥ 8 weeks (Figure 4).
Concerning the RR for successful treatment, we found a gradual decrease in the RR when the postoperative interval increased. If treated ≥ 4 weeks, the RR was 1.0 (CI: 0.8–1.2) compared with < 4 weeks. The RR for success if treated ≥8 weeks (compared with treatment < 8 weeks) was 0.6 (CI: 0.3–0.95) (Figure 5).
In the group of patients where the treatment started ≥ 8 weeks, 7 of 14 infections healed (Table 1). Of the 6 THR infections, 2 infections healed despite retention of the prosthesis. In the remaining 4 patients, the THR had to be extracted, resulting in resolution of infection in 2. Of the 8 TKR infections, 5 healed. In the remaining 3, the implant was removed, and 2 of these infections resolved. Thus, altogether, in 11 of 14 prostheses the infection eventually healed despite an interval of more than 8 weeks after implantation. 7 of these 11 infections became infection-free without extraction, even with an interval of almost 1 year postoperatively.
In the 6 hematogenous THR and TKR infections, we found no correlation between the duration of symptoms and the results of the treatment with retention of the prosthesis.
In the infections that were difficult to treat, more debridements were needed, but the failure rate increased (Table 2).

8 of the 11 infections that were debrided for a third time healed, but when a fourth debridement was necessary none of the 3 infections healed.
ASA score, type of infection, host and wound staging, number of interventions, or preoperative infection parameters such as fever or laboratory values were similar in the success group and the failure group. We found no relation between the result of the treatment and the causative bacteria. Neither a difference in the result of the treatment between gram positive and gram-negative bacteria, or between staphylococci and streptococci. We found no influence of the use of rifampicin, which was added to the treatment protocol since 2004. There was no association between the MIC of gentamicin for the causative bacteria and the success rate of the treatment.

Discussion

We found good results if we treated deep-infected stable THRs and TKRs by debridement and retention of the prosthesis, in combination with systemic and local antibiotics. Removal of a stable, well-fixed implant is associated with high morbidity and mortality. So the treatment of an infected implant without removal is attractive. Since the results vary greatly, with success rates between 31% and 100% retention of the implant remains controversial.(6,11-16) The controversy is, however, less focused on the treatment with retention as such, and more on the interval after which the results become too bad.
We therefore focused on the delay in the start of treatment in relation to the results. We could quantify the risks for failure and success of the treatment postoperatively up to 10 weeks. The treatment had a low and almost unchanged risk of failure up to an interval of 4 weeks, and thereafter it increased every week (Figure 4). The RR for successful treatment showed a gradual decrease in these first weeks, and after 8 weeks there was significantly more risk of failure (as indicated by its CI) (Figure 5). The smaller numbers of infections treated after 10 weeks justifies limitation of our conclusions to only these intervals.
When we consider the balance between the disadvantages of the removal of a prosthesis on the one hand and the failure rate of a treatment with retention on the other, we prefer a retention up to 8 weeks postoperatively.
Several authors reported a cut-off of only a few days of symptoms for successful retainment of a prosthesis after a deep infection.(17-19) Most authors consider a postoperative interval of 2–4 weeks to be the maximum period that a prosthesis can be retained.(20,21) Some studies have suggested that this period could be longer. Currently, the algorithm by Zimmerli et al. is the one most commonly used.(7,11,22,23) In their algorithm, they limit the acceptable period of symptoms to a maximum of 3 weeks if the prosthesis is stable, the soft tissues are in good condition, and an antibiotic with activity against biofilm is available.
However, confusingly, in the literature 2 different periods are used in protocols: the duration of symptoms and the postoperative period since implantation ("joint age").(13) The recent guideline of the Infectious Diseases Society of America uses a limit for in situ treatment of 3 weeks of symptoms, and also a joint age of less than 30 days.(22) We regard the postoperative period as a clearer guideline, since the onset of symptoms of a deep infection is very difficult to estimate in clinical practice. Another argument is that these infections must be regarded as having been caused by contamination during the implantation operation.
In some patients, an even higher risk of failure with an interval of more than 8 weeks might be acceptable. In 14 of our patients who were treated after such a long interval, the infection resolved in 7 cases with retention of the prosthesis, and in 4 after extraction, so the result for healing of infection was 11 out of 14. This result is comparable with results in the literature when the postoperative infection was treated with early extraction, with reimplantation in 1 or 2 stages.(25,26)
As we do, Kim et al. also advocated repeated debridement, but their advice was to stop and remove the prosthesis after 4 attempts.(20) In our patients, no infections healed when debridement was performed more

than 3 times, so in our hands extraction after 3 debridements appears to be justified.

Comparing our results with those in the literature, they are relatively good, despite an often long postoperative interval. One explanation for this could be the consistent use of local antibiotic carriers in our treatments, with gentamicin-loaded beads or collagen. The high local gentamicin concentration is important, since the infection is probably limited to recently operated tissues, which will be accessible for the debridement and local antibiotic carriers.

In 28-year study period, our treatment protocol remained essentially unchanged, focusing on retainment of the implant and on the use of local antibiotic carriers, to supplement systemic antibiotics. The main advantage of gentamicin-PMMA beads is a high local antibiotic concentration at the site of the infection, without systemic toxic side effects.(27) A disadvantage of beads is the space needed, and they have to be removed with an extra operation. The removal operation can, however, be performed with a smaller incision, permitting local inspection, deep cultures, and if necessary a repeated debridement. Gentamicin collagen fleeces have the advantage that they are resorbable and have less volume, which makes insertion easier, especially in TKR infections, and removal unnecessary. In our experience, however, a disadvantage of fleeces is increased wound secretion up to 6 weeks postoperatively, causing difficulties in wound control. Also, they release most of their antibiotics in the first 1–2 hours of implantation.(28)

During the study period, we did not replace polyethylene components or modular heads, but we have been doing this routinely since 2010. We found more *S. aureus* infections than CNS infections. This can be explained since *S. aureus* causes more acute infections and CNS with a lower virulence are more frequently seen in low-grade and late infections.(13,23)

We found no association between the result of the treatment and the MIC of gentamicin for the bacteria, but even high MIC values are not an absolute contraindication for the use of gentamicin beads or fleeces. These MIC values are based on systemic gentamicin treatment, and in a treatment with local antibiotic carriers the local gentamicin concentrations are much higher, up to several hundreds of µg/mL.(27,29,30)

The present study had some limitations. It was a retrospectively studied cohort, and the treatment was performed by several orthopedic surgeons. We combined the data on postoperative infections of THRs and TKRs, and the cohort included both primary and revision implantations. However, there were also some strong points: the patients were treated at a single center with an almost unchanged protocol for 28 years, treating the infections in the same way with local antibiotics. Although several debridements were performed by different colleagues at the department, a single surgeon was responsible for the treatment of the patients over the whole period. As our department has a “last-resort function” in treating infections, loss to follow-up was low. We were able to follow the patients for at least 1.5 years if they were still alive. Instead of presenting the results of the treatment as percentages of healing, as in most studies in the literature, we were able to calculate the relative effect of the treatments to show the estimation uncertainty, especially regarding variation in the postoperative interval.

In conclusion, treatment of THR or TKR infections can be performed with retention of the prosthesis when the implant is stable. The use of local antibiotics is probably helpful. In postoperative infections, a gradually increased risk of failure of the treatment should be weighed by each surgeon against the disadvantages of removal of the prosthesis. We consider a risk of failure of 50%, if treatment occurs within 8 weeks in most patients, to be acceptable. This approach can still be considered for even longer postoperative intervals in some patients, although we cannot identify these specific patients.

JG and GW treated the patients, designed the study and wrote the manuscript. DJ collected the data of the medical records, completed the follow-up, and performed statistical analyses. AK supervised and helped in the statistical analysis. All authors contributed to interpretation of the data and to the revisions of the manuscript. No competing interests declared.

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2-stage revision of 120 infected hip and knee prostheses using gentamicin-PMMA beads

DMC Janssen
J Geurts
LM Jütten
GHIM Walenkamp

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Chapter III

2-stage revision of 120 deep infected hip and knee prostheses using gentamicin-PMMA beads. Results after 5 (2–20) years

Daniël M C Janssen, Jan A P Geurts, Liesbeth M C Jütten, and Geert H I M Walenkamp
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Abstract

Background and purpose. A 2-stage revision is the most common treatment for late deep prosthesis-related infections and in all cases of septic loosening. However, there is no consensus about the optimal interval between the 2 stages.

Patients and methods. We retrospectively studied 120 deep infections of total hip (n = 95) and knee (n = 25) prostheses that had occurred over a period of 25 years. The mean follow-up time was 5 (2–20) years. All infections had been treated with extraction, 1 or more debridements with systemic antibiotics, and implantation of gentamicin-PMMA beads. There had been different time intervals between extraction and reimplantation: median 14 (11–47) days for short-term treatment with uninterrupted hospital stay, and 7 (3–22) months for long-term treatment with temporary discharge. We analyzed the outcome regarding resolution of the infection and clinical results.

Results. 88% (105/120) of the infections healed, with no difference in healing rate between short- and long-term treatment. 82 prostheses were reimplanted. In the most recent decade, we treated patients more often with a long-term treatment but reduced the length of time between the extraction and the reimplantation. More reimplantations were performed in long-term treatments than in short-term treatments, despite more having difficult-to-treat infections with worse soft-tissue condition.

Interpretation. Patient, wound, and infection considerations resulted in an individualized treatment with different intervals between stages. The 2-stage revision treatment in combination with local gentamicin-PMMA beads gave good results even with difficult prosthesis infections and gentamicin-resistant bacteria.

Introduction

The incidence of prosthetic joint infection is 1–2%, and it may be increasing. It is difficult to ascertain what the "true" incidence is, since arthroplasty registries appear to miss one-third of the infections, and complex linkages with other databases are necessary to obtain reliable data.(1)

Successful eradication of deep prosthesis infection has been reported using 1-stage and 2-stage revision, with comparable infection-free rates of approximately 90%.(2-4) Even so, in most countries the preferred treatment for infection-related prosthesis loosening and late infections is a 2-stage revision: repeated debridements and antibiotic treatment for a prolonged period are possible before reimplantation or other reconstruction is performed. Stepwise decisions can be made for a particular patient and infection during treatment. There is, however, no evidence in the literature concerning the optimal length of time between extraction of the prosthesis and reimplantation.(4,5)

At our institution, early and delayed deep prosthetic infections (joint age < 2 years) are preferentially treated in situ with retention of the prosthesis if there is no loosening. The results in 90 patients have been published.(7) We treat the remaining cases (where extraction of the infected prostheses is indicated) with a 2-stage revision and use local antibiotic carriers in the form of gentamicin-PMMA beads. During the course of the present study, some changes in the treatment protocol were introduced, but the cornerstone of the treatment remained unchanged: the use of a local antibiotic carrier in the form of gentamicin beads to give a high local antibiotic concentration in exudate and tissues.(6)

The main goal of this study was to determine the results of treatment of the infection of prostheses with a 2-stage revision using gentamicin-PMMA beads, with either a short interval or a long interval between the first-stage operation and the second-stage operation.

Patients and methods

In this retrospective observational study, we analyzed a cohort of all proven deep postoperative and hematogenous infections of total hip prostheses (THR) and total knee prostheses (TKR) that had been treated with extraction of the prosthesis at our center from January 1986 through December 2010. This covered early or delayed deep infections in cases of loosening, all late infections (> 2 years after implantation), all patients with poor soft-tissue conditions (fistula, gross indurations, large abscesses), patients who were significantly immunocompromised, and patients with persistent infections after previous treatment with debridement, antibiotics, and implant retention (DAIR) at another hospital.

Baseline characteristics (Table 1)

Over a period of 25 years, we treated 312 THR and TKR prosthesis infections. The results of the treatments in which 89 prostheses were not extracted but treated in situ with DAIR have already been described by us.(7) In 167 infections the prosthesis was extracted including all late infections (> 2 years after implantation), and infections with loosening (< 2 years). We excluded 47 prostheses as follows: in 18 patients, the Mayo criteria (8) for deep infection were not met, 6 patients had already undergone an extraction at another center, 23 patients had been treated with a 1-stage revision because a low grade infection had not been diagnosed prior to the operation (but only afterwards from intraoperative cultures). We included the remaining 120 infected prostheses in 120 patients (51 men and 69 women). The age of the patients at the extraction was 62 (30–82) years. There were 95 THR infections (34 primary THRs and 61 septic or aseptic revisions) and 25 TKR infections (10 primary TKRs and 15 septic or aseptic revisions). 6 of the infections were hematogenous: 5 THR and 1 TKR. We considered deep infections as being hematogenous infections when there was no sign of prosthesis infection in the period since implantation, in combination with a distant focus of infection.(9)

Table 1. *Baseline characteristics of patients and infections, with results of infection treatment*

	Total n = 120	Success n = 105	Failure n = 15
Patient characteristics			
Age	62 (30–82)	62 (30–82)	62 (44–80)
Sex: M / F	51 / 69	42 / 63	9 / 6
ASA-1	35	63	2
ASA-2	61	57	4
ASA-3	24	15	9
Morbidities			
Smoking	24	22	2
Alcohol abuse	12	10	2
Diabetes mellitus	18	13	5
Inflammatory disease	4	3	1
Malignancy	9	8	1
Immunosuppression	1	1	0
Renal failure (dialysis)	7	3	4
Heart failure	22	18	4
Host score according to McPherson			
A - Uncompromised	60	55	5
B - Compromised	54	47	7
C - Significantly compromised	6	3	3
Host score according Cierny			
Uncompromised	43	39	4
Compromised	77	66	11
Prosthesis and infection characteristics			
Total hip	95	84	11
Total knee	25	21	4
Indication index prosthesis			
Primary arthroplasty	44	39	5
Aseptic revision	49	41	8
Septic revision	27	25	2
Infection period			
Postoperative infections, n	114	100	14
joint age, weeks	108 (2–1,407)	117 (2–779)	46 (3–1,407)
Hematogenous infections, n	6	5	1
symptoms, days	41 (7–48)	46 (7–84)	(48)
Soft tissue			
Not involved	73	63	10
Induration	2	2	0
Abscess or fistula	45	40	5
Infection score according to McPherson			
Early postoperative (< 4 weeks)	4	2	2
Hematogenous infections	5	4	1
Late postoperative (> 4 weeks)	111	99	12
Local score according to McPherson			
Grade 1 - Uncompromised	37	34	3
Grade 2 - Compromised	66	57	9
Grade 3 - Significantly compromised	17	14	3
Infection type according to Zimmerli			
Early postop. + hematogenous [a]	9	4	5
Delayed exogenous [b]	45	37	8
Delayed hematogenous [b]	1	1	0
Late exogenous [c]	61	59	2
Late hematogenous [c]	4	4	0
Preoperative blood markers			
ESR > 20 mm/h	103	88	15
CRP > 10 mg/L	91	79	12
Leucocytes > 11 x 10^9/L	16	13	3
Temperature ≥ 38.0°	24	21	3
Systemic antibiotics			
Preoperatively, n	34	27	7
I.v. postoperatively, days	35 (2–132)	32 (2–132)	51 (20–125)
Oral postoperatively, days	76 (21–221)	76 (21–221)	78 (38–166)
Total days of postoperative therapy	104 (32–251)	101 (29–251)	128 (65–203)

a < 3 months; b 3–24 months; c > 2 years

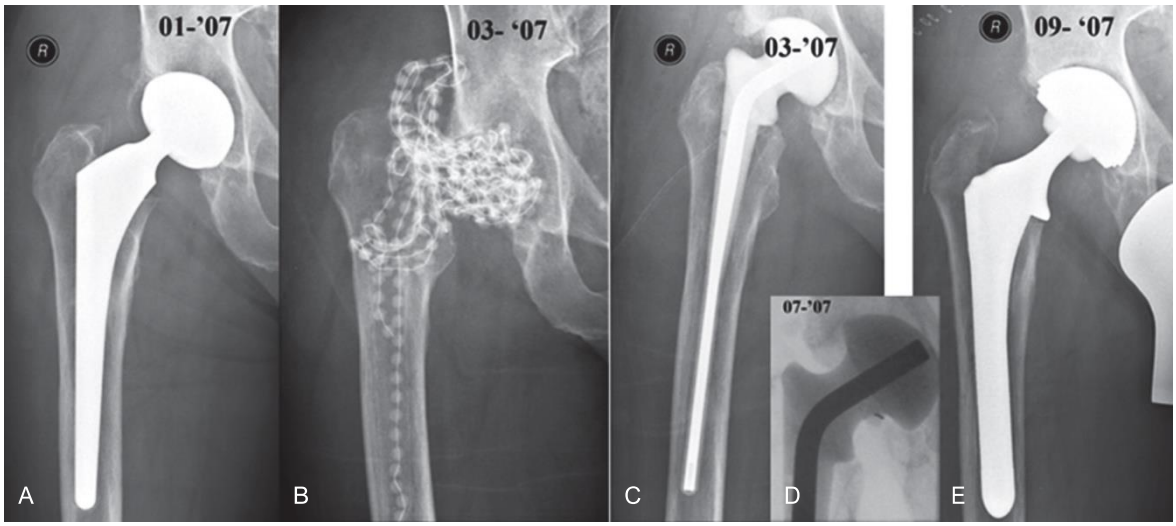

Figure 1. *2-stage revision. A. Infected hip prosthesis in a 68-year-old woman. After extraction of the prosthesis, implantation of 360 gentamicin-PMMA beads for 2 weeks (B), then exchange to a spacer for 2 months (C). D. Puncture for culture, after 2 weeks of "antibiotic holiday". E. After re-admission, extraction of the spacer and reimplantation of a total hip.*

Prostheses were considered to be infected when the Mayo criteria were fulfilled: growth of the same microorganism in 2 or more cultures from synovial fluid or periprosthetic tissue, pus in synovial fluid or at the implant site, histological evidence of acute inflammation in periprosthetic tissue, or a sinus tract communicating with the prosthesis. (8) The interval between implantation of the prosthesis and the start of treatment of the infected prosthesis (i.e. joint age) in 114 postoperative infections was 25 (0.5–325) months. In the 6 hematogenous infections, the duration of symptoms was 41 (7–84) days (Table 1).

Surgical treatment

Our treatment consisted of extraction of the prosthesis, debridement, and implantation of gentamicin-PMMA beads for 2 weeks. If necessary, the debridement and implantation of beads for 2 weeks was repeated. Finally, we performed either a reimplantation, a girdlestone procedure, an arthrodesis, or an amputation. The gentamicin-PMMA beads had a diameter of 7 mm and contained 7.5 mg gentamicin sulfate per bead, in the form of chains (60 or 30 beads, Septopal; Merck GmbH, Darmstadt, Germany; Biomet GmbH, Berlin, Germany). We implanted as many beads as possible in all infected and contaminated tissues to create a high local concentration of gentamicin: median 296 (60–540) beads for THR and 228 (60–420) beads for TKR (Figure 1). The wound was tightly closed in layers, to keep the gentamicin containing exudate in the wound. To avoid leakage of a hematoma to the subcutaneous layers, a deep and a subcutaneous drain was left for a few days. The deep drain was passive, with just syphoning in the first day to avoid too much blood loss and with suction after 1 day to reduce the hematoma. The beads did not stick through the skin but were removed in the second operation after 2 weeks. After they became available, we used antibiotic-loaded spacers, but never for primary infection treatment—only to make space between the articulating bones when patients were discharged for a long period of time between treatments, to improve stability and facilitate reimplantation.

2-stage procedure

After 1 or more treatment periods of debridement with 2 weeks of gentamicin beads, it was decided whether the final reimplantation or reconstruction should be performed during the same hospital stay (short-term

treatment), or whether it would be better to postpone it and discharge the patient, observing the result at outpatient visits (long-term treatment).

With short-term treatment, we treated 63 patients (57 THRs and 6 TKRs). 35 patients had 1 single debridement and treatment with beads for 2 weeks, 22 had 2 debridements, and 6 had 3 or 4 debridements. In 30 of the 57 THRs and 2 of the 6 TKRs, a reimplantation after short-term treatment was performed, whereas in 31 patients no reimplantation followed (in 27 hips, a girdlestone; and in 4 knees, an arthrodesis) (Figure 2). For short-term treatment, the median interval between extraction and reimplantation or other reconstruction was 14 (11–47) days.

In long-term treatment, after extraction of the prosthesis, debridements, and the initial antibiotic therapy, patients were discharged without a prosthesis but with the availability of a spacer (since 2003), increasingly more often with a spacer. In these cases, full weight bearing was not allowed, but patients were encouraged to move the joint cautiously. Patients were discharged home for a median period of 5.5 (3–21) months. This period was used to finish the antibiotic treatment and to check that there was no recurrence of the infection over a period without systemic antibiotic treatment (the “holiday period”).(10)

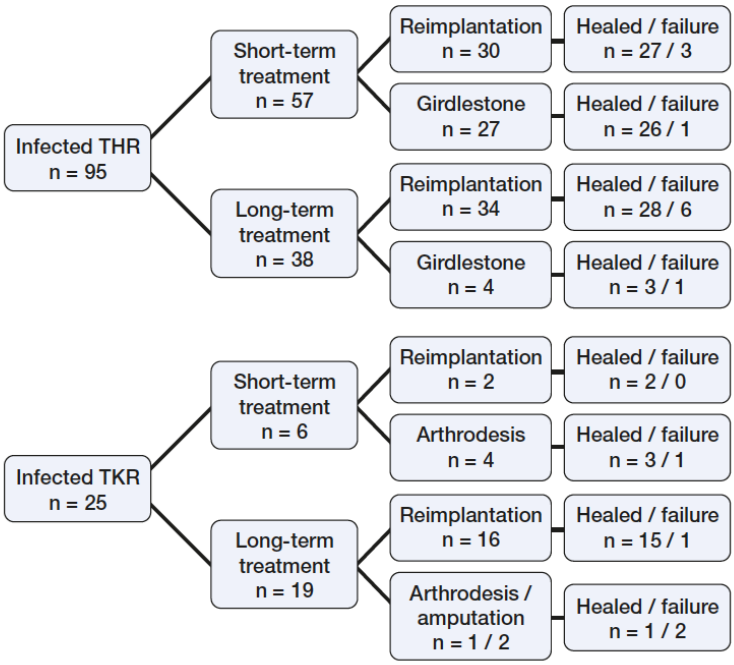

Figure 2. *Diagram of treatments with data on reimplantation and healing of the infection.*

Table 2. *Causative microorganisms*

Microorganism	Total	Success	Failure
CNS (β-lactamase positive)	32	27	5
CNS (β-lactamase negative)	14	14	0
Staphylococcus aurues (β-lactamase positive)	18	14	4
Staphylococcus aurues (β-lactamase negative)	8	8	0
MRSA	1	1	0
Streptococcus spp.	7	7	0
Enterococcus spp.	3	1	2
Enterobacter spp.	4	4	0
Pseudomonas aeruginosa	5	3	2
Cutibacterium acnes	4	4	0
Negative culture without antibiotics	8	8	0
Negative culture with antibiotics	2	2	0
Polymicrobial	14	12	2
Total	88	78	10

When using spacers, an antibioticfree period of at least 2 weeks was used before puncture of the joint for deep bacterial culture. After re-admission, the patients were reoperated. The spacer, if present, was removed, deep tissues were cultured, and the reconstruction was prepared, which in fact functioned as a final re-debridement. The reimplantation or arthrodesis was then performed, or (if healing of the infection was uncertain) gentamicin-PMMA beads were implanted again while waiting for the deep-tissue culture results.
57 patients had long-term treatment (38 THRs and 19 TKRs). 1 debridement was performed for 37 infections and 2 or more debridements were performed for 20 infections. Before the introduction of spacers in our clinic in 2003, we had discharged 16 patients without a prosthesis (15 girdlestone hips and 1 knee pseudarthrosis) for an interval of 5–21 months. After the introduction of spacers, we could more often give long-term treatment, since the joint, especially in knees, was more stable. We used spacers in 23 of 38 THR treatments and in 18 of 19 TKR treatments. After long-term treatment, reimplantation of a prosthesis was performed in 34 of 38 hips and in 16 of 19 knees. A girdlestone procedure was performed in 4 THR patients; in the knee patients, 1 arthrodesis and 2 amputations were performed (Figure 2). Altogether, in long-term treatment the median interval between extraction and reimplantation of the prosthesis was 7 (3–22) months. Patients with negative culture results received amoxicillin/clavulanate as broad-spectrum antibiotic treatment.

Systemic antibiotics

The surgical treatment was combined with systemic antibiotics, intravenously during hospitalization and continued, if possible, orally after discharge from hospital. The choice of antibiotic was based on the resistance pattern of the deep tissue cultures and after consulting a microbiologist with an interest in orthopedic infections.
We stopped the oral antibiotic treatment at the outpatient clinic when clinical and laboratory parameters had been normal for at least 4 weeks. The intravenous antibiotic treatment was given for a median period of 35 (2–132) days, followed by oral treatment for 76 (21–221) days. Median total antibiotic treatment was 105 (21–251) days.

Microbiology

Swabs and synovial fluid were taken for bacterial culture and multiple tissue cultures. Cultures were taken preoperatively and peroperatively in antibiotic-free patients, so antibiotics were given peroperatively after all the samples had been taken. The samples were cultured in the microbiology laboratory for at least 3 weeks to detect slow-growing microorganisms, and minimal inhibitory concentrations (MICs) of gentamicin were determined for all bacteria detected. We found a beta-lactamase producing coagulase-negative staphylococcal strain to be the most frequent causative microorganism (32 of 120 infections) (Table 2). In 10 patients, the peroperative cultures showed no growth. 2 of these patients had ongoing antibiotic therapy.

Mixed flora caused 14 infections, with bacterial species in many combinations and coagulase-negative staphylococcal species and streptococcal species being the most frequent. The MIC of gentamicin for the causative bacteria was ≤ 2 µg/mL in 62 infections, 2–15 µg/mL in 15 infections, 16–64 µg/mL in 21 infections, and ≥ 64 µg/mL in 7 infections (Table 3). In 31 of the 120 cases, a change in the original causative bacterium to another bacterium occurred during treatment.

Follow-up

During the hospital stay, we checked the infection parameters ESR, CRP, and leukocyte differentiation twice a week, and also liver and kidney function once a week, to monitor infection healing and possible toxicity of the antibiotic treatment.

Table 3. *Minimal inhibitory concentrations (MIC) of gentamicin with results of treatment*

MIC gentamicin (µg/mL)	Total	Success	Failure
< 2	62	53	9
2–15	17	15	2
16–64	24	21	3
> 64	7	6	1
Negative cultures	10	10	0
	120	105	15

The follow-up period started at the first operation for deep infection and the end of the follow-up period was either the date of the last outpatient clinic visit or the date of death, whether or not it was related to the infection. We extended the follow-up by contacting the family doctor when possible. Mean follow-up was 5 (2–20) years, with the exception of 8 patients who had died before the 2-year follow-up.

The treatment of infection was considered to be successful when the infection was healed at follow-up, that is, when there were no clinical or radiological signs of recurrence after the treatment of the infection with or without a prosthesis in situ. We considered that laboratory parameters had normalized when CRP and WBC counts were normal at 2 subsequent controls, and when the ESR was less than 30 mm/h in patients without systemic diseases. Failure was assumed if the patient never became infection-free, if there was relapse of the infection, or if amputation was necessary.

Data analysis and statistics

Data are presented as either median (range) or mean (SD). All patients and types of infections were scored according to classifications by ASA, Cierny, McPherson, and Zimmerli.(5,11,12) Success and failure rates were analyzed according to these staging's and classifications.

We analyzed the influence on infection healing of the characteristics of patients and infections, the index operation, blood markers, and the pathogen (including the MIC value for gentamicin). 8 patients died within 24 months of the start of the treatment for infection, 3 of them without healing of the infection. 5 other patients died within 24 months because of poor health, but this was not related to the infection and there were no symptoms of infection.

Survival analysis of healing of infection was performed with Kaplan-Meier curves (Figure 3). In this analysis, the event of healing was considered to be the moment when the patient had been free of infection for 6 months after termination of surgical and antibiotic treatment. This period was chosen as a clinically relevant period when the diagnosis of healing could be considered to be a safe one. It corresponds well with the time after the treatment when any relapse of infection in any of the patients had already occurred: 5.5 months.

Right-censored observations were included: this indicated, for example, patients who left the study before becoming infection-free, or that the end of the observation period had been reached. The ASA classification and the infection classification according to Zimmerli are represented as Kaplan- Meier curves, also with censoring (Figures 4 and 5).

A log-rank test was performed to determine the influence on the outcome of the characteristics of patients and infections, the index operation, blood markers, and the pathogen (including the MIC value for gentamicin). Any p-value of less than

0.05 was considered to be significant. In determining differences between the short-term and long-term treatment groups, chi-square test was used to analyze categorical variables and the Mann-Whitney U-test was used for analysis of continuous variables. Cox regression analysis was used to analyze confounding factors. We used SPSS version 22.0 for Windows.

Results

Successful treatment of the infections was achieved for 105 of 120 prostheses (88%). 15 treatments failed: 3 of the failures were never infection-free, and in 12 failures a relapse of the infection occurred (after apparent healing) between 15 and 156 days after completing the antibiotic treatment (Figure 2). 8 of the 15 failures became free of infection after another treatment regimen, in 2 of the patients with re-extraction of the reimplanted prosthesis, increasing the healing rate for infection to 94%.

In THRs, 84 of 95 infections healed. Reimplantation was performed in 64 of these 95 THRs: after 30 short-term treatments and after 34 long-term treatments, and for these reimplanted prostheses infection was resolved in 55 of the 64 patients.

In TKRs, 21 of 25 infections healed. Reimplantation was performed in 18 of the 25 patients: after 2 short-term treatments and 16 long-term treatments. The 5 arthrodeses consolidated and the infection healed.

6 hematogenous infections are included in the above results. Of these, one TKR treatment failed, and 5 hematogenous THR infections were successfully treated.

We analyzed the effect on resolution of the infection of Zimmerli classification, ASA classification, primary or revision prosthesis, and whether the infected revision itself was performed for aseptic loosening or because of infection. We found similar age and sex distributions in the success group and the failure group. There was similar outcome for infections of primary and revision prostheses. Irrespective of the original indication for the infected revision (aseptic or septic cause), there was also similar outcome.

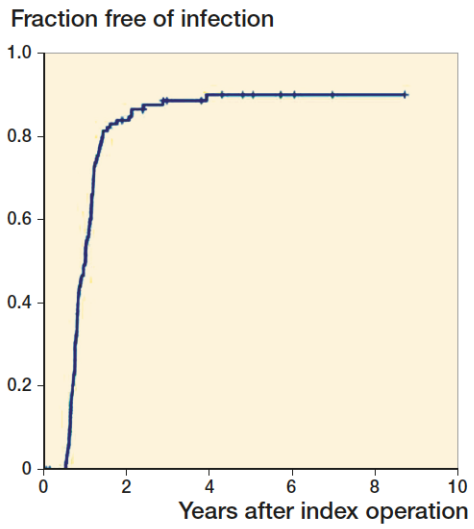

Figure 3. *Kaplan-Meier curve depicting the time-to-event analysis with right-censoring, for healing of the infection. The event is healing for 6 months since the completion of the operative and antibiotic treatment.*

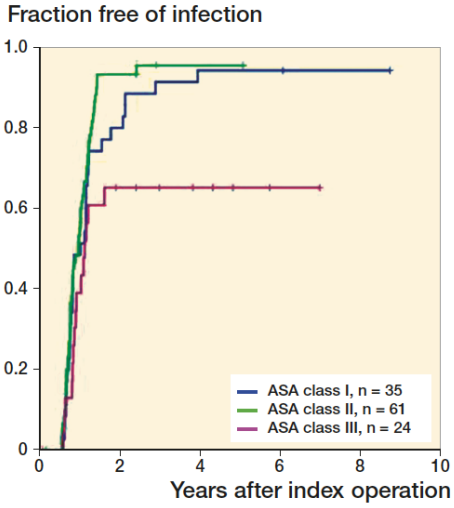

Figure 4. *Kaplan-Meier curves for infection healing with strata for ASA classifications.*

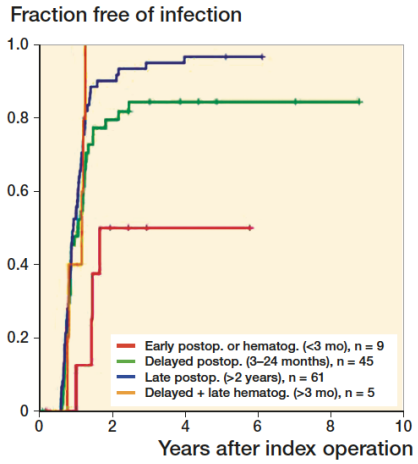

Figure 5. *Kaplan-Meier curves for infection healing with strata for the classification of type of infection according Zimmerli.*

We found a higher risk of failure for ASA score 3 than for ASA score < 3 ($p = 0.01$) (Figure 4), and for early postoperative infections according to Zimmerli ($p = 0.006$) (Figure 5). The influence of patient characteristics on these effects was analyzed but it was not statistically significant (i.e. had no confounding effect).

In the 114 surgical site infections (SSIs), the earlier the infection was treated postoperatively (i.e. the shorter the joint age), the more the treatment failed ($p = 0.001$). In the 6 hematogenous infections, the duration of the symptoms (7–84 days) had no influence on the outcome. Other patient and wound scores, other comorbidities, and preoperative infection parameters (fever, laboratory values) had no influence on the outcome.

We found no association between the result of the treatment and the primary causative bacterial species, no difference between the group of gram-positive and gram-negative bacteria, no difference between Staphylococcus species and Streptococcus species, and not more failures in beta-lactamase producing bacteria. In the last 5 years of the study period, more causative bacteria had a MIC value for gentamicin of ≥ 16 µg/mL compared to the previous 20-year period, but the success rate for resolution of the infection was the same for high and low MIC values ($p = 0.08$). During 31 of 120 treatments, the causative microorganism changed to other bacteria, and these treatments failed more often than treatments where no shift in causative bacteria occurred. The therapeutic use of antibiotics just before the start of treatment of the infection had no influence on the outcome (Table 1). The length of the intravenous antibiotic treatment postoperatively and the total length of postoperative antibiotic treatment was shorter in the successfully treated patients than in the failures ($p = 0.02$ and $p = 0.05$).

The long-term treatment group included more difficult-to-treat infections: more acute infections with a shorter prosthetic joint age and less loosening of the prosthesis ($p = 0.03$). The causative bacteria more often had a MIC value of ≥ 16 µg/ mL ($p = 0.007$). In THR, in the long-term treatment group the wound score was worse, with more fistulae ($p < 0.001$). More debridements were necessary ($p < 0.001$). TKRs were given long-term treatment more often than THR ($p = 0.001$). Despite the more difficult-to-treat infections being given long-term treatment, these cases were reimplanted more frequently than those in the short-term treatment group ($p < 0.001$).

If success was defined as the combination of resolution of infection and successful reimplantation, the treatment was successful in 71 of 120 patients (60%), and failed in 49 patients. The failure rate was higher in patients with an ASA score of 3 than in those with an ASA score of 1 or 2 ($p = 0.01$), in more compromised patients according to McPherson ($p = 0.02$), and in those with more compromised soft tissue according to Cierny ($p = 0.009$). Other covariates had no influence on the risk of failure.

Discussion

In our long study period of 25 years, the treatment of infected prostheses has gradually changed worldwide. In the 1960s, the common therapy for osteomyelitis or prostheses infections after debridement was suction-irrigation for 4–6 weeks.(13) The development of gentamicin-PMMA beads in the 1970s, a better alternative to suction-irrigation systems, made it possible to close the wound and mobilize the patient. The main advantage was a high antibiotic delivery locally without systemic toxicity.(6) The introduction of spacers improved the technical possibilities for the 2-stage approach.(14) They largely facilitate the reimplantation but have an inferior release of antibiotics compared to beads, due to a largely reduced surface area and different composition of the gentamicin-loaded carrier.(15,16)

Table 4. *Results in the literature of treatment of infected THR and TKR with hand-made or commercial antibiotic-loaded PMM beads*

First author	Year	No.of prostheses	THR/TKR	Follow-up (years)	Healed (%)	Weeks to reconstruction	Beads
Hovelius (17)	1979	3	THR	1.5	100	3–4	Septopal®
Walenkamp (18)	1983	41	THR/TKR	1.1	85	2–4	Septopal®
Scott (19)	1993	7	TKR	?	100	6	hand-made
Garvin (20)	1994	16	THR	5.7 (2–10)	100	?	hand-made
Lenoble	1995	32	THR	5 (2–11)	92	45–82	Septopal®
Haddad	2000	50	THR	5.8	92	3–52	hand-made
Taggart	2002	33	THR/TKR	5.8 (5–9.3)	97	40 (9–156)	hand-made
Hsieh	2004	70	THR	4.9 (2–8)	93	?	hand-made
Hoad-Reddick (21)	2005	38	TKR	4.7 (2–10)	89	?	hand-made
Stockley	2008	114	THR	6.2 (0.2–15)	88	28 (9–96)	hand-made
Chen	2009	48	THR	5.6 (2–14)	96	23 (9–104)	both
This series	2015	120	THR/TKR	5 (2–20)	88	4 (1.6–102)	Septopal®

We therefore used spacers not as a tool for local antibiotic therapy, but only to make space between the articulating bones when patients were discharged during the time interval between stages in the long-term treatment group (to facilitate reimplantation) and, like other authors, continued the therapeutic application of antibiotic-loaded PMMA beads (Table 4).(17,22,23) Hsieh et al. (2004) compared 2 consecutive groups of patients treated with either antibiotic-loaded spacers or beads, and found that the treatment of 58 infected hip prostheses with spacers did not result in more persistent infection than in treatment of 70 prostheses with beads, despite the inadequate antibiotic elution. Patients had better function in the intervening period, but not any more at the final review after eventual reimplantation.(24)

In this study, we excluded the infected prostheses that could be treated in situ with DAIR. (7) Thus, the more difficult infections remained; these would be more likely to have a lower success rate.(25,26) In spite of this, the success rate is comparable to that in the literature in unselected cases: 67–95%.(2,3,27,28) In most studies on revision of infected prostheses, there is an important surgical selection bias: the easy infections are treated more and more with 1-stage revision and the difficult infections with 2-stage revision.(2,27,29,30) Most algorithms show a trend of having a less aggressive reimplantation strategy in cases with more difficult-to-treat bacteria, worse immune capacity, more complex reconstruction, or more failed treatments in the past.(30,31) In our 2-stage revision approach, comparable choices are made by us in an individualized treatment approach, based on the seriousness of the infection, but taking into account the physical and psychological condition of the patient.

We preferred long-term treatment in the difficult cases to give the greatest chance that the infection would be resolved prior to reimplantation. Long-term treatments were made easier because we could use spacers to improve the function during the long discharge period and to facilitate reimplantation. Especially in TKR, the longer interval with spacers is helpful in recovering soft tissue before reimplantation can be safely performed.

We performed more long-term treatment procedures in the last decade of the study period (Figure 6), but at the same time reduced the interval between the first and last stages (Figure 7), as also described by Hansen and Spangehl (2004).(32) The interval between extraction and reimplantation of the prosthesis, as used in 2-stage treatments, has some advantages: soft tissue has more time to recover, the systemic antibiotic therapy can be completed, and the result of treatment be observed in an antibiotic-free period. At the outpatient check-ups during the treatment, some patients appear to be insufficiently fit for reimplantation—invoking the risk of failure—or they refrain from further treatment. So we agree with other authors who have also used such a stepwise approach.(3,31–33)

Some authors have reported that treatments with an interval between extraction and reimplantation of less than 1 year have a better functional outcome than with longer intervals.(34,35) However, the intervals might probably be reduced for both hips and knees: good results were described for a 2-stage approach with an interval of not more then 2—6 weeks for a selected population without any antibiotic resistance of the pathogen or significant compromise regarding the patient.(5,36).
The higher risk of failure that we found in patients with an ASA score of 3, high McPherson score, or renal failure has been confirmed by other author.(28) We also found that preoperative laboratory values and body temperature were not predictive of failure of the infection treatment.(37,38)

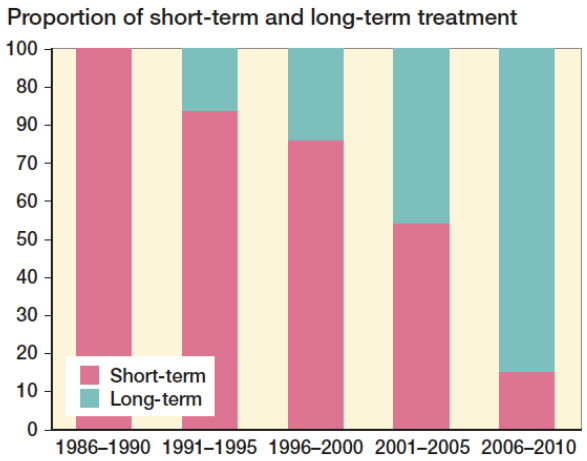

Figure 6. *Proportions of short-term and long-term treatment in each 5-year period: increase in long-term treatment with time.*

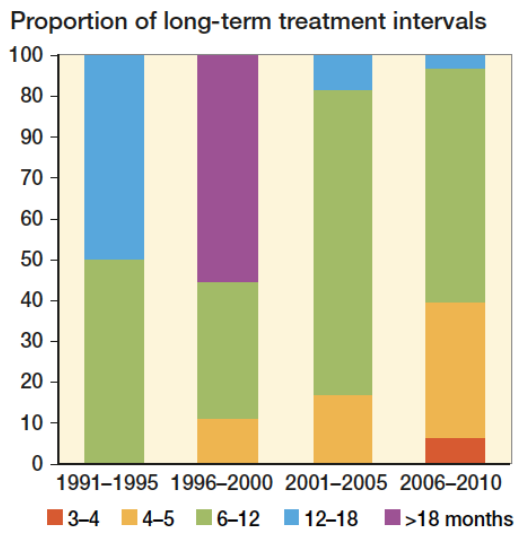

Figure 7. *Intervals (months) of long-term treatment in four 5-year periods, with shorter intervals in more recent years.*

Our finding that there was a higher risk of failure in patients with a lower prosthetic joint age contrasts with some other reports.(30,36). But the early infections included in our study were subject to negative selection where extraction would be necessary, since the easier-to-treat infections were mainly treated in situ with a DAIR procedure, as already published.(7) The most frequent causative microorganism in our series was coagulase-negative staphylococcus (CNS), as also published by others regarding late chronic infections.(4,36) If a shift in the causative bacteria cultured occurred during the treatment, the failure rate was higher—especially if a shift occurred to a more difficult-to-treat pathogen, for instance, MRSE or Pseudomonas aeruginosa. We have found no other data on the influence of the MIC value on the treatment of prosthesis infection in the literature, except Salvati et al. (1986), who described a patient where a treatment with gentamicin-PMMA beads was successful, despite a gentamicin MIC value of 250 µg/mL for *P. aeruginosa.*(39)

The total length of antibiotic treatment following removal of the infected implant was between 4 weeks and 6 months, and substantially longer in the case of failures. There is no conclusive evidence regarding the ideal duration of antibiotic therapy; the recent literature recommends antibiotic therapy for between 2 and 6 weeks.(5,31,40)

Discontinuation of antibiotic treatment prior to reimplantation (the “holiday” period) is used to ensure that the infection has been eradicated or to increase the reliability of a culture before or during reimplantation.(10) This antibiotic-free period, however, varies in the literature between only 2–4 days (5) and 6 weeks.(33) With easy-to-treat microorganisms, some authors have advised continuation of the antibiotic treatment up to the final reimplantation or reconstruction.(30)

Our study had some limitations. It was retrospective, and we did not study the functional outcome. Due to the long period covered, some changes in the treatment protocol were unavoidable, such as the introduction of spacers. Since our department functions as a tertiary referral center for orthopedic infections, patients were probably selected who were more often difficult to treat compared to other centers, which may have influenced the rate of reimplantation. The strength of our study was the consistent use of gentamicin-PMMA beads as a highly bactericidal tool used locally to achieve infection healing. Also, the 2-week stepwise

treatment approach, inherent in proper use of the beads, was unaltered during the entire study period. The choice of interval between the 2 stages was based on surgical judgement of risk factors that did not change importantly in time, although the length of the interval gradually became shorter. This is the largest series in which the results of treatment of prosthesis infections with antibiotic-loaded PMMA beads have been studied, even more so when considered in combination with our previously published series of non-extracted prostheses: 210 prosthetic infections in total.

In conclusion, treatment of an infected prosthesis is a patient- and infection-dependent procedure where matching is important, in our case balancing between short-term treatment and long-term treatment. With our treatment, the healing of the infection is the first and main goal; reimplantation is only performed if infection healing is appropriate. As in other series, our results are based on a choice of therapeutic modalities without sound evidence from well-designed trials. The use of local antibiotics with gentamicin-impregnated PMMA beads is helpful, especially in bacteria with high gentamicin resistance. In our treatments, spacers are mainly useful to maintain better joint function with long interval periods, and they should preferably not be used for treatment of the infection itself, since they do not result in high exudate levels of gentamicin. In our approach, there was a tendency to give more high-risk infections long-term treatment, but with a shorter interval between the 2 stages.

GW and JG treated the patients. GW and DJ designed the study. DJ collected the data from the medical records and completed the follow-up. DJ and LJ performed the statistical analysis. All the authors contributed to interpretation of the data and to writing and revision of the manuscript.

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A retrospective analysis of deep surgical site infection treatment after instrumented spinal fusion with the use of supplementary local antibiotic carriers

DMC Janssen
M Kramer
J Geurts
LW van Rhijn
GHIM Walenkamp
P Willems

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Chapter IV.

A Retrospective Analysis of Deep Surgical Site Infection Treatment after Instrumented Spinal Fusion with the Use of Supplementary Local Antibiotic Carriers

Daniël M.C. Janssen, Maud Kramer, Jan Geurts, Lodewijk v Rhijn, Geert H.I.M. Walenkamp, Paul C. Willems
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Abstract

Background. There is no generally established treatment algorithm for the management of surgical site infection (SSI) and non-union after instrumented spinal surgery. In contrast to infected hip- and knee-arthroplasties, the use of a local gentamicin impregnated carrier in spinal surgery has not been widely reported in literature.

Patients and methods. We studied 48 deep SSI and non-union patients after instrumented spine surgery, treated between 1999 and 2016. The minimum follow-up was 1.5 years. All infections were treated with a treatment-regimen consisting of systemic antibiotics and repetitive surgical debridement, supplemented with local gentamicin releasing carriers.
We analysed the outcome of this treatment regimen with regard to healing of the infection, as well as patient- and surgery-characteristics of failed and successfully treated patients.

Results. 42 of the 48 (87.5%) patients showed successful resolution of the SSI without recurrence with a stable spine at the end of treatment.
36 patients' SSI were treated with debridement, local antibiotics, and retention or eventual restabilization of the instrumentation in case of loosening. 3 patients were treated without local antibiotics because of very mild infection signs during the revision operation. 3 patients were treated with debridement, local antibiotics and removal of instrumentation. One of these patients was restabilized in a second procedure.
Infection persisted or recurred in 6 patients. These patients had a worse physical status with a higher ASA-score. *Staphylococcus aureus* was the most frequent causative microorganism.

Interpretation. Debridement and retention of the instrumentation, in combination with systemic antibiotics and the addition of local antibiotics provided a successful treatment for SSI and non-union after instrumented spinal fusion.

Introduction

The incidence of surgical site infection (SSI) after spinal surgery ranges from 2 to 12%, depending on diagnosis, surgical approach, use of spinal instrumentation, and the complexity of the procedure.(1-4)

SSI is a devastating complication that leads to prolonged treatment, with the need for subsequent reoperations and substantially increased overall health care costs. Moreover, SSI after instrumented spinal surgery is associated with higher rates of morbidity and mortality, and has a negative impact on functional clinical outcome.(5-7)

There is no generally established treatment protocol for the management of deep SSI after instrumented spinal surgery. As we know from SSI after general fracture management with osteosynthesis, instrumentation is preferably left *in situ* as preservation of stability is crucial to allow for bony union while the infection is managed. Likewise, in spinal fusion, as long as bony union has not occurred, stable instrumentation material should be left *in situ* in order to prevent loss of correction or development of pseudarthrosis due to mechanical instability.(8,9) After bony consolidation, the instrumentation can be removed if necessary in a second stage for complete cure of the infection.(10)

Gentamicin impregnated carriers

Polymethylmethacrylate (PMMA) or bone cement is able to release admixed powdery substances if these are soluble in water and heat stable during polymerization.(11) Buchholz admixed four heat stable antibiotic powders with bone cement and found that, except for tetracycline, the antibiotics indeed were released by a diffusion process for at least 2 weeks in a bactericidal concentration.(11) Subsequently, many handmade and commercially made combinations of antibiotics and bone cements were tested, of which gentamicin in combination with Palacos bone cement provided the best antibiotic release after implantation and best stability during polymerization.(12-14)

Gentamicin is very suitable for prevention or treatment of orthopedic infections since it exhibits a broad antibacterial spectrum including gram-positive and gram-negative germs, and a good bactericidal effect in low concentrations with a low rate of resistances development.(15)

Gentamicin-impregnated bone cement was first introduced to prevent SSI after cemented implantation of joint arthroplasties.(16) Once on the market, it was also used to treat osteomyelitis by filling bone cavities after debridement. Because small beads of bone cement mixed with antibiotics were proven to be more effective, non-absorbable gentamicin impregnated PMMA beads (Septopal®) were commercially produced for local antibiotic treatment of infections, by admixing gentamicin to the liquid monomer and polymer powder, in combination with glycine as a filler to promote the gentamicin release.(17)

In view of the successful treatment with these non-absorbable drug carriers, endeavours were made to develop absorbable materials that no longer needed removal.(18) Because collagen carriers are fully absorbed, gentamicin-collagen products can be used in one-step surgical procedures.

Pharmacokinetic release models have shown that the release of gentamicin from collagen fleeces is more rapid and less longstanding as compared to PMMA-beads.(19) Both carriers have shown a high local gentamicin concentration without toxic concentrations in the blood.(19,20)

Although commonly used in prosthetic joint infections (PJI) and osteomyelitis,(21-23) the use of antibiotic loaded carriers in SSI after instrumented spinal fusion has not been widely reported.(8, 20-24) Because of good results in the use of gentamicin PMMA-beads or fleeces in the treatment of prosthetic joint infections we incorporated local gentamicin in the treatment of SSI after instrumented spinal fusion.(22,23)

The aim of this study was to assess the treatment results after the use of a local gentamicin impregnated carriers, supplementary to operative debridement and administration of systemic antibiotics for SSI without union after instrumented spinal fusion, with an in-depth analysis of failed cases.

Material and methods

This is a retrospective case-series analysis of all non-union, deep SSI patients after instrumented thoracolumbar spinal fusion procedures that had been performed in the Department of Orthopedics of the Maastricht University Medical Centre, a secondary and tertiary academic referral center for spinal pathology and for orthopaedic infections, from January 1999 up to December 2015.

Diagnosis

The diagnosis of surgical site infection was based on criteria as described by the CDC (Centre for Disease Control and prevention) and the Dutch national PREZIES network (*prevention of hospital infections through surveillance*). (25,26). According to these criteria, a SSI was considered to be deep if it presented at the site of the operation with involvement of subfascial tissue.(25)

Patients

We diagnosed 62 (6,9%) deep surgical site infections (30 female, 32 male) out of 898 instrumented spinal surgery procedures (14 anterior approach, 884 posterior approach). 14 patients (4 female, 10 male) with an SSI were excluded from analysis: One patient had been treated for spondylodiscitis as the index operation, two patients did not receive treatment for SSI because of terminal illness and one patient was excluded because of loss to follow up. 10 patients had a late SSI with bony union of the spondylodesis. These 10 union SSI were all successfully treated with removal of the instrumentation and with additional local antibiotic administration in 2 patients. We included 48 patients (47 after posterior instrumented spinal fusion and 1 after anterior instrumented spinal fusion).

Treatment protocol

Deep infections of instrumented spinal fusion without bony consolidation, and without signs of implant loosening were treated by surgical debridement, systemic antibiotics, irrigation and implant retention (DAIR), in combination with application of

antibiotics loaded carriers (gentamicin PMMA-beads or fleeces).

In case of instrumentation loosening and a unstable spine, new instrumentation was inserted for restabilisation (Figure 1).

The procedure consisted of debridement with removal of loose bone graft material, pulsed lavage with at least 3 litres of Ringer lactate and either retention, removal or restabilisation of the instrumentation depending on the stability of the instrumentation and spine. The patients were treated with systemic and local antibiotic therapy. As local antibiotic carrier we preferably used gentamicin PMMA beads with a diameter of 7 mm, containing 7.5 mg gentamicin sulphate, in chains of 30 or 60 beads (Septopal®, Merck GmbH, Darmstadt, Germany; Biomet GmbH, Berlin, Germany). We packed as many beads in the infected tissues as tensionless wound closure would allow in order to create a high local gentamicin concentration. Wounds were fully closed and the gentamycin beads were removed in a second procedure 2 weeks later.

Multiple tissue samples were taken for bacteriological cultures right before the administration of systemic antibiotics. The samples were cultured in the microbiology laboratory for at least 2 weeks in order to also detect slow growing microorganisms. The minimal inhibitory concentration (MIC) value for gentamicin of the specific bacteria strain was then determined.

If infection signs had not resolved, the gentamicin beads were removed, a new debridement was performed, and new beads were left behind during a second procedure 2 weeks later.

In case of very mild intraoperative infection signs, one debridement was considered to be enough and only gentamicin collagen fleeces were used as local gentamicin impregnated antibiotic carrier. Gentamicin collagen fleeces (Septocoll®, containing 116 mg gentamicin sulphate and 350 mg gentamicin crobephate in 320 mg

equine collagen fleece with a size of 10x8 cm; Merck GmbH, Darmstadt, Germany; Biomet GmbH, Berlin, Germany) were applied before closing the wound, to prolong the period with local antibiotics and obviate the need for removal of the beads in another operation.

Spinal instrumentation was removed if, infection persisted according to clinical and laboratory parameters despite one or more treatment periods of 2 weeks with gentamicin beads. In case of instability because of non-union as determined intraoperatively by visible motion across the fused segment(s) and the absence of bony continuity on inspection, the spine was restabilized directly with renewed instrumentation.(27, 28) The infection treatment was then continued with the local application of gentamicin PMMA beads and intravenous administration of antibiotics.

Figure 1. *Treatment algorithm of deep surgical site infection after instrumented spinal fusion. * 45/48 infections were treated with debridement of the wound and a local gentamicin carrier (gentamicin fleeces in 3 SSI and gentamicin PMMA beads in 42 SSI) and 3/48 were treated without local gentamicin treatment because of very mild signs of a deep infection during operation. β 3/4 failures died sepsis-related during infection treatment. One failure presented with a recurrent infection with the same initial microorganism (Staphylococcus aureus) that was successfully treated with removal of the instrumentation and local gentamicin PMMA beads. α 1 failure died during infection treatment because of sepsis. # 1 failure was a recurrence of infection of the anterior instrumentation that occurred more than 3 years after the secondary restabilization. This patient died during the second infection treatment because of a poor health condition (terminal metastatic renal cancer).*

Systemic antibiotics

The surgical treatment was combined with high dosed systemic antibiotics, usually for a period of approximately 3 months, including a minimum of two weeks intravenous administration during hospitalization and continued oral administration after discharge from the hospital. The choice and exact duration of the systemic antibiotic treatment was decided on an individual basis and based on antibiotic resistance pattern of the causative bacteria by consultation of a microbiologist specialized in orthopaedic infections.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell counts (WBC) were measured twice a week during hospitalisation and at all outpatient control visits for monitoring of infection healing. We considered these parameters as normal when CRP and WBC counts were within the normal range (CRP <10 mg/L; WBC<10,000 cells/mcL) at 2 subsequent outpatient control visits, and the ESR was decreased to less than 30 mm/h in patients without systemic disease and cessation of systemic antibiotic treatment.

Outcome

The treatment was considered successful when at follow up the infection was eradicated (normalized inflammatory blood markers and no clinical signs of infection) with a stable spine by instrumentation or by osseous fusion. Failure was diagnosed if the infection was not eradicated.

The subjective outcome (disabling back pain or leg pain with limitations in activities of daily living (ADL)) were noted as “yes” or “no” at the end of the follow-up at the outpatient clinic.

The follow-up period started at the date of the first operation for infection, and ended on the date of the last outpatient clinic visit, the last contact with the family doctor or the date of death. The minimum follow up was 1.5 year or shorter in case of death, either related or not to the SSI.

Statistical analysis

Patient characteristics (gender, age, BMI, smoking status, comorbidities, ASA-score, medication, trauma, radiation therapy, blood values, revision surgery, interval between primary surgery and infection treatment, antibiotic use and MIC genta) and operation variables (primary indication, combination surgery with a second incision, fused levels, anatomical levels, graft use, cage use, dural tear, microorganism and soft tissue condition) were presented as either median with total range, or as mean with standard deviation (SD).

Additionally, the odds ratios (OR) with 95% confidence intervals (CI) were calculated for all patients’ characteristics and risk factors for poor treatment outcome. The Mann Whitney U test was used to analyse differences of continuous variables between successfully treated patients and failures.

SPSS (version 17.0) was used for all statistical calculations.

Results

48 patients with a deep SSI without bony union were treated, of which 42 (87.5%) were treated successfully. Recurrence of infection occurred after more than 2 years in 2 patients. Four patients died during infection treatment because of sepsis (Table 1 and Figure 2).

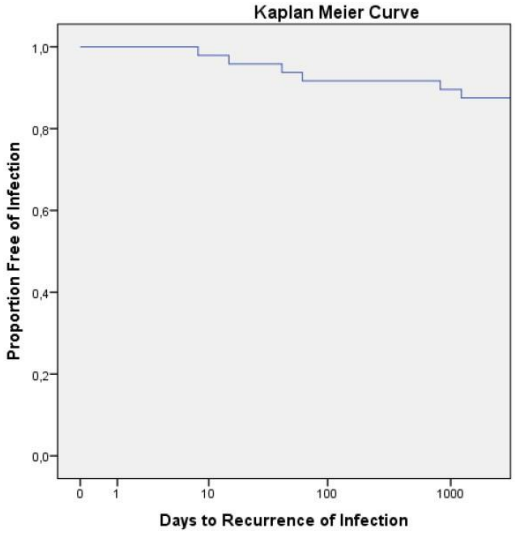

Figure 2. Kaplan-Meier survival curve that represents the proportion of all patients free of infection after treatment for deep SSI after instrumented spinal fusion.

37 of 48 patients were treated with debridement, retention of the stable instrumentation (DAIR), and local antibiotics: 33 of these 37 were treated successfully, while 4 failed.

8 of the 48 patients were treated with DAIR after restabilization of loose instrumentation of which 3 without local antibiotics, because there were minimal signs of infection intraoperatively.

Instrumentation was removed without spinal restabilization in 3 of the 48 patients, as the lumbar spine was considered stable after instrumentation removal. These 3 cases were all treated with gentamicin PMMA beads. One of these patients required anterior restabilization in a second stage after 2 periods of treatment with gentamicin PMMA beads (Figure 1).

6 of the 48 patients were treated with only one debridement, and 24 were treated with 2 debridements, whereas 15 needed 3 debridements and only 3 patients needed 4 debridements of the wound.

The median time of systemic intravenous antibiotic treatment was 41 (3-95) days, followed by oral treatment for another 43 (0-196) days. The median total antibiotic therapy time was 84 (6-251) days. Oral antibiotic treatment at the outpatient clinic was stopped when clinical and laboratory parameters were considered as normal. *Staphylococcus aureus* was found as the most frequent (24/48) causative microorganism (Table 2). There was no significant difference with respect to causative microorganism between the failed and the successfully treated patients. No relation could be found between the MIC value for gentamicin of the causative bacteria and the success rate of the infection treatment (Table 3).

5 of the 6 patients (83%) in whom the infection treatment failed had an ASA-score >2 compared to only 12 of 42 (29%) in the population with a successful treatment.

There were no other isolated patient characteristics or operation-related variables that differed significantly between the 6 patients in whom the infection treatment failed and the 42 successfully treated patients (Table 2 and 3).

At the end of follow-up, 5 patients (10.4%) complained of residual disabling back pain with limitations in ADL, 2 patients (4.2%) complained of persisting disabling leg pain with limitations in ADL, and 3 patients (6.3%) had

residual disabling back and leg pain with limitations in ADL.

In summary, 87.5% (42/48) of all patients with a SSI and non-union after an instrumented spinal procedure where treated successfully with a treatment regimen consisting of systemic antibiotics and repetitive surgical debridement supplemented with local gentamicin releasing carriers. 8% (4/48) died during infection treatment because of sepsis and in 4% (2/48) recurrence of infection occurred after more than 2 years.

Table 1. *Details of the patients*

Diagnosis	pathogen	Interval (days)	Debride-ments	FU	Outcome	Treatment	Subjective outcome
Fracture with threatened myelum	S. viridans	1	1	1062	Success	Debridement, restabilization, no local AB	Back pain & disabilities in ADLs
Scoliosis (degenerative)	E. Coli	8	2	962	Success	DIAR + fleeces	Back pain, no disabilities in ADLs
Degenerative spondylolysis	E. coli	9	3	1159	Success	DIAR + beads	Back pain, no disabilities in ADLs
Failed previous spine surgery	S. Aureus	9	3	1195	Success	DIAR + beads	No pain or disabilities in ADLs
HNP with threatened myelum	S. Aureus	9	3	882	Success	DIAR + beads	Disabilities in ADLs without pain
RIP with threatened myelum	E. Coli	10	2	875	Success	Debribement, restabilization + beads	Leg pain & disabilities in ADLs
RIP with threatened myelum	mixed flora	10	2	1277	Failure	Removal implants + beads, restabilization in second procedure	No pain or disabilities in ADLs
Failed previous spine surgery	mixed flora	11	1	371	Success	DIAR, no local AB	No pain or disabilities in ADLs
Fracture with threatened myelum	E. cloacae	12	2	1185	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	mixed flora	12	3	1402	Success	DIAR + beads	No pain or disabilities in ADLs
Fracture without threatened myelum	S. Aureus	12	2	733	Success	Debribement, restabilization + beads	Back pain, no disabilities in ADLs
Spinal stenosis	S. Aureus	13	3	406	Success	DIAR + beads	No pain or disabilities in ADLs
Fracture without threatened myelum	E. coli	13	2	884	Success	DIAR + beads	Disabilities in ADLs without pain
Fracture without threatened myelum	S. Aureus	13	2	1092	Failure	DIAR + beads	Back pain, no disabilities in ADLs
Degenerative spondylolisthesis	E. Coli	13	1	1106	Success	DIAR + fleeces	No pain or disabilities in ADLs
Degenerative spondylolisthesis	E. cloacae	14	2	519	Success	DIAR + beads	Back & leg pain & disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	14	4	1163	Success	DIAR + beads	Back & leg pain, no disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	15	3	251	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	15	3	1007	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. pyogenes	15	1	1334	Success	DIAR + beads	Back pain & disabilities in ADLs
Spinal stenosis	S. Aureus	15	2	1483	Success	DIAR + beads	Back pain & disabilities in ADLs
Lytic spondylolisthesis	mixed flora	16	2	1037	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	16	3	1039	Success	DIAR + beads	Back pain, no disabilities in ADLs
Pseudoartrosis	S. Aureus	16	1	1219	Success	Removal implants + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. mitis	17	3	762	Success	DIAR + beads	No pain or disabilities in ADLs
Scoliosis (degenerative)	CNS	17	2	854	Success	DIAR + beads	Leg pain & disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	17	3	745	Success	Removal implants + beads	Back & leg pain & disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	18	1	8	Failure	DIAR + beads	Dead
Degenerative spondylolisthesis	mixed flora	18	2	1466	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	CNS	19	3	976	Success	DIAR + beads	No pain or disabilities in ADLs
Fracture without threatened myelum	S. Aureus	20	1	15	Failure	DIAR + beads	Dead
Fracture with threatened myelum	E. coli	20	2	275	Success	DIAR + beads	Disabilities in ADLs without pain
Degenerative spondylolisthesis	mixed flora	20	4	741	Success	Debribement, restabilization + beads	Back & leg pain & disabilities in ADLs
Fracture without threatened myelum	S. Aureus	21	2	777	Success	DIAR + beads	No pain or disabilities in ADLs

Diagnosis	pathogen	Interval (days)	Debride-ments	FU	Outcome	Treatment	Subjective outcome
Spinal stenosis	S. Aureus	21	3	1065	Success	DIAR + beads	No pain or disabilities in ADLs
Fracture without threatened myelum	S. Aureus	21	2	5017	Success	Debribement, restabilization + beads	Back pain & disabilities in ADLs
Fracture with threatened myelum	E. Coli	22	1	1474	Success	DIAR + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	23	2	1187	Success	DIAR + beads	No pain or disabilities in ADLs
Spinal stenosis	S. Aureus	30	1	2770	Success	DIAR + beads	Back pain, no disabilities in ADLs
RIP with threatened myelum	S. Aureus	31	1	42	Failure	DIAR + beads	Dead
RIP with threatened myelum	CNS	33	2	583	Success	Debribement, restabilization + beads	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	48	2	62	Failure	Debribement, restabilization + beads	Dead
RIP with threatened myelum	S. Aureus	63	2	191	Success	DIAR + beads	Back pain, no disabilities in ADLs
Degenerative spondylolisthesis	G. elegans	66	1	458	Success	DIAR + beads	Leg pain, no disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	66	4	848	Success	DIAR + fleeces	Back pain & disabilities in ADLs
Fracture without threatened myelum	P. acnes	90	1	1112	Success	DIAR, no local AB	No pain or disabilities in ADLs
Degenerative spondylolisthesis	S. Aureus	141	2	378	Success	Debribement, restabilization + beads	No pain or disabilities in ADLs
Fracture without threatened myelum	S. pneumoniae	186	2	1080	Success	DIAR + beads	Back pain, no disabilities in ADLs
Failed previous spine surgery	negative	265	1	1035	Success	Removal implants + beads	Back pain & disabilities in ADLs
Fracture without threatened myelum	P. aeruginosa	308	1	1336	Success	Removal implants, no local AB	No pain or disabilities in ADLs
Failed previous spine surgery	negative	345	2	2920	Success	Removal implants + beads	Back & leg pain & disabilities in ADLs
Fracture without threatened myelum	S. intermedius	402	2	1058	Success	Removal implants, no local AB	Back pain & disabilities in ADLs
Failed previous spine surgery	P. acnes	525	1	2105	Success	Removal implants, no local AB	Back pain & disabilities in ADLs
Fracture without threatened myelum	P. acnes	531	1	1157	Success	Removal implants, no local AB	No pain or disabilities in ADLs
Degenerative disc disease/discopathy	P. acnes	691	1	1550	Success	Removal implants, no local AB	Back pain & disabilities in ADLs
Fracture with threatened myelum	P. acnes	934	1	811	Success	Removal implants, no local AB	No pain or disabilities in ADLs
Scoliosis, idiopathic	S. Aureus	2723	1	756	Success	Removal implants, no local AB	No pain or disabilities in ADLs
Fracture with threatened myelum	CNS	3292	1	1862	Success	Removal implants, no local AB	No pain or disabilities in ADLs

Table 2. *Operation related variables*

Operation-related variable	Overall	Successful (42) Infection treatment	Failed (6) Infection treatment	Odds-ratio	95%CI	*p*-value
Operation-indication						
Fracture	12 (25.0%)	10 (23.8%)	2 (33.3%)	0.625	0.099-3.935	0.616
Degenerative spine-disorders	23 (47.9%)	21 (50.0%)	2 (33.3%)	2.000	0.329-12.123	0.451
Spinal stenosis	4 (8.3%)	4 (9.5%)	0	1.520	0.073-31.693	0.787
Spinal metastasis	5 (10.4%)	3 (7.1%)	2 (33.3%)	0.154	0.020-1.212	0.076
Failed previous spine surgery	2 (4.2%)	2 (4.8%)	0	0.803	0.035-18.677	0.891
Other	3 (6.3%)	3 (7.1%)	0	1.152	0.053-24.993	0.928
Combined surgery (second incision)	3 (6.3%)	3 (7.1%)	0	1.152	0.053-24.993	0.928
Levels fused						
Number	2.6 (1 – 9)	2.6 (1 – 9)	3.2 (1 – 6)	1.042	0.683 – 1.590	0.848
Anatomical levels						
Thoracal	7 (14.6%)	5 (11.9%)	2 (33.3%)	0.270	0.039-1.876	0.186
Thoracolumbar	8 (16.7%)	6 (14.3%)	2 (33.3%)	0.333	0.050-2.239	0.258
Lumbar	19 (39.6%)	18 (42.9%)	1 (1.7%)	3.750	0.402-34.957	0.246
Lumbosacral	13 (27.1%)	12 (28.6%)	1 (1.7%)	2.000	0.211-18.957	0.546
Thoracosacral	1 (2.1%)	1 (2.4%)	0	0.470	0.017-12.813	0.654
Bonegraft	41 (85.4%)	37 (88.1%)	4 (66.7%)	3.700	0.533-25.679	0.186
Other than Autograft	10 (20.8%)	7 (16.7%)	3 (50.0%)	0.200	0.033-1.203	0.079
Cage used	33 (68.8%)	31 (73.8%)	2 (33.3%)	5.636	0.903-35.189	0.064
Dural tear	7 (14.6%)	6 (14.3%)	1 (16.7%)	0.833	0.082-8.433	0.877
Microorganisme						
Staphylococcus Aureus	24 (50.0%)	19 (45.2%)	5 (83.3%)	0,165	0,018-1,539	0,114
Cutibacterium acnes (spp.)	1 (2.1%)	1 (2.4%)	0	0.470	0.017-12.813	0.654
Coagulase negative staphylococcus	3 (6.3%)	3 (7.1%)	0	1.152	0.053-24.993	0.928
Enterobacter species	9 (18.8%)	9 (21.4%)	0	3.687	0.190-71.525	0.389
Streptococci species	5 (10.4%)	5 (11.9%)	0	1.907	0.094-38.778	0.675
Polymicrobial	6 (12.5%)	5 (11.9%)	1 (16.7%)	0.676	0.065-7.024	0.743
Soft tissue condition						
Intact	2 (4.2%)	1 (2.4%)	1 (16.7%)	0.122	0.007-2.268	0.158
Open (wet)	43 (89.6%)	38 (90.5%)	5 (83.3%)	1.900	0.176-20.560	0.597
Abcess/ fistula	3 (6.3%)	3 (7.1%)	0	1.152	0.053-24.993	0.928

Table 3. *Patient related variables*

Patient-related variables	Overall (58)	Successful (52) infection treatment	Failed (6) infection treatment	Odds-ratio	95%CI	*p*-value
Man	22 (45.8%)	19 (45.2%)	3 (50.0%)	0.826	0.149-4.576	0.827
Woman	26 (46.6%)	23 (46.2%)	3 (50.0%)	1.211	0.219-6.705	0.827
Age	58.3 (19-83)	56.3 (19 – 83)	65.1 (37 – 80)			0.177*
BMI	28.2 (17.7 – 41.3)	28.3 (17.7 – 41.3)	28.1 (22.4 – 34.7)			0.327*
Obesity (BMI > 30)	19 (39.6%)	18 (42.9%)	1 (16.7%)	3.750	0.402-34.957	0.246
Smoking	23 (47.1%)	21 (50.0%)	2 (33.3%)	2.000	0.330-12.123	0.451
Comorbidities						
Diabetes	6 (12.5%)	5 (11.9%)	1 (16.7%)	0.676	0.065-7.024	0.743
Pulmonary disease	14 (29.2%)	13 (31.0%)	1 (16.7%)	2.241	0.238-21.150	0.481
Rheumatic disease	8 (16.7%)	7 (16.7%)	1 (16.7%)	1.000	0.101-9.928	1.000
Cardiac disease	11 (22.9%)	9 (21.4%)	2 (33.3%)	0.546	0.086-3.471	0.521
Malignancy (active)	6 (12.5%)	4 (9.5%)	2 (33.3%)	0.211	0.029-1.533	0.124
ASA I	9 (18.8%)	9 (21.4%)	0	3.687	0.190-71.525	0.389
ASA II	21 (43.8%)	20 (47.6%)	1 (16.7%)	4.546	0.488-42.307	0.183
ASA III	17 (35.4%)	12 (28.6%)	5 (83.3%)	0.080	0.008-0.758	0.028
Medication						
Use Steroid	8 (16.7%)	6 (14.3%)	2 (33.3%)	0.333	0.050-2.239	0.258
Use of immunosuppressive	5 (10.4%)	3 (7.1%)	2 (33.3%)	0.154	0.020-1.212	0.076
Trauma patient	7 (14.6%)	5 (11.9%)	2 (33.3%)	0.270	0.039-1.876	0.186
Polytraumatic injury	2 (4.2%)	2 (4.8%)	0	0.803	0.035-18.677	0.891
UCI admission	3 (6.3%)	2 (4.8%)	1 (16.7%)	0.250	0.019-3.280	0.291
Radiation therapy after initial spine surgery	5 (10.4%)	3 (7.1%)	2 (33.3%)	0.154	0.020-1.212	0.076
Blood values preop.						
CRP	169.3 (6 – 584)	152.6 (6 – 584)	298.5 (209 – 414)			0,412*
ESR	57.7 (10 – 120)	55.7 (10 – 112)	75.2 (47 – 120)			0,617*
Leucocytes	16.1 (1 – 87)	16.5 (1 – 87)	12.8 (6.9 – 16.4)			0.904*
Temperature preop.	37.8 (36.4 – 40.0)	37.8 (36.4 – 40.0)	38.1 (36.4 – 39.5)			0.912*
Primary	35 (72.9%)	30 (76.2%)	5 (83.3%)	0.500	0.053-4.739	0.546
Revision	13 (27.1%)	12 (23.8%)	1 (16.7%)	2.000	0.211-18.957	0.546
Interval surgery to start infection symptoms	33 (1 – 186)	34 (1 – 186)	24 (10 – 49)			0.667*
Preop. use of AB	28 (58.3%)	24 (57.1%)	4 (66.7%)	0.667	0.110-4.050	0.660
Postop. duration AB iv	38.0 (6 – 95)	39.4 (8 – 95)	29.3 (6 – 59)			0.275*
Postop. duration AB oral	48.6 (0 – 196)	47.7 (14 – 133)	55.0 (0 – 196)			0.412*
Postop. duration AB total	78.7 (6 – 251)	79.3 (15 – 201)	75.2 (6 – 251)			0.242*
MIC-genta	27.5 (0.50 – 64)	30.6 (0.5 – 64)	1.5 (0.5 – 2.0)			0.509*
Total number of gentamicin-beads	123.3 (0 – 240)	121.4 (0 – 240)	142.5 (120 – 180)			0.412*

*= Mann Withney U test

Discussion

The present study analyzed treatment of SSI and non-union in patients who underwent instrumented fusion of the thoracolumbar spine, with the use of gentamicin impregnated carriers. 42 of the 48 (87.5%) patients showed successful resolution of infection with stable spinal fusion at the end of treatment, without recurrence of infection after a minimum of 1.5 years follow-up.

Although direct comparison with results from other studies in literature is difficult due to the heterogeneity of patient populations, the success rate of treatment in the present study appears to be quite high., Chen et al. reported an implant salvage success rate of 80.4% (41 in 51 patients) with repeated debridements (mean 1.7), systemic antibiotics, with adjunctive antibiotic-impregnated PMMA beads in 20 patients after a 2-year follow-up in patients with SSI after posterior spinal instrumentation.

In 8 of the 41 (19.5%) successfully treated cases, solid fusion was not achieved. Furthermore, only 2 out of 10 patients (20%) who underwent debridement with implant removal showed stable fusion. Unfortunately, the success rate of a subgroup of 20 patients who were treated with antibiotic loaded PMMA beads was not reported separately.(29)

Glassman et al. treated 22 patients with SSI after instrumented spinal fusion with multiple debridements

(mean 4.7), retention of the instrumentation, and antibiotic (tobramycin and vancomycin) impregnated PMMA beads. No patient showed recurrence of wound infection. Fusion was apparently solid in 14 patients, probable in four patients and nonunion occurred in one patient.(30)

Compared to previous studies in which antibiotic carriers have not been used, the present study shows a favourable success rate. Kowalski et al. reported a success rate of 71% in 28 early onset spinal implant infections with retention of instrumentation, and 84% in 32 late onset spinal implant infections with operative debridement and removal of instrumentation.(31) Collins et al. reported a cure rate of 40% in 15 acute infections following instrumented spinal fusion with long-term (systemic) antibiotics and debridement with retention of the instrumentation.(6) The lower eradication rates observed in these studies clearly illustrate the added value of local antibiotic carriers in infection treatment after instrumented spine surgery in our opinion.

Kim et al. treated 20 patients with SSI between 1 and 5 months after instrumented spinal surgery with implant removal and wide debridement to clear the infection, despite the risk of disc space collapse and loss of normal lordosis. The infection was eradicated in all 20 patients after a minimum follow up of 2 years, but instability and/or pseudarthrosis at the fused segments was observed in 14 patients, thus resulting in a poor clinical outcome.(32)

Several other supplemental procedures have been reported in the treatment of SSI after instrumented spinal fusion aside from the use of antibiotic impregnated PMMA beads, such as continuous suction irrigation, vacuum-assisted wound closure, or local tissue flap coverage. These studies are difficult to compare, because of the different treatment procedures. However the success rate of the present study is in the higher range of the success rates reported for these alternative supplemental procedures. Rohmiller et al. treated 28 patients with post-operative spinal infection with one operative session consisting of incision, drainage and closed suction irrigation. 75% of infections were resolved without recurrence after an average follow-up of 22.3 months.(33)

Mehbod et al. achieved a clean closed wound after an average follow-up of 10 months (6-24 months) in all of 20 patients with SSI after spinal fusion, treated with an average of 1.8 (1-8) debridements prior to a vacuum-assisted wound closure procedure, and an ultimate VAC removal procedure in which the wound was closed over drains.(34) Labler et al. needed to exchange or remove the instrumentation in 12 of 13 infections after instrumented spinal surgery treated with vacuum assisted closure of the wound (15-40 months follow-up). One patient developed a recurrence infection at follow-up.(35) Sierra-Hoffman et al. reported a cure rate of 89% for early onset instrumented spinal infection in 19 patients by debridement with retention of the instrumentation, drainage and packed open with antibiotic solution soaked gauze and loose retention sutures. All patients returned to the operating room for follow-up debridement and closure over drains after 2-3 days, followed by systemic antibiotic administration. They noted a cure rate of 100% with no relapses for at least 3 years after therapy was reported in 7 late onset infections with removal of the instrumentation and 1 or 2 debridements.(4)

In this study, a mean number of 2.3 (1-4) operations were needed including the removal of the PMMA beads, mostly a minor operation. Picada et al. reported that one-third of 26 patients required four or more debridements before obtaining a clean wound for closure.(36) Mehbod et al. reported a mean number of 3.25 (3-10) visits to the operating room to obtain a closed wound with vacuum-assisted wound closure in 20 patients.(34)

In the present study 16.7% of the patients complained of residual disabling back pain at the end of the follow up, and 27.1% patients in total experienced limitations in activities of daily living because of residual back and/or leg pain. Similar to most studies in literature, our patients showed a less satisfactory outcome after instrumented spinal fusion with SSI compared with control groups without infection.(29,37,38)

We found *Staphylococcus aureus* (*S. aureus*) to be the most frequent (24/48) causative microorganism of SSI. This is comparable to literature.(6,29,33,39) International literature reports suggest an increasing prevalence of MRSA (8, 32), but MRSA was not cultured in our patients. This may be the result of the strict MRSA policy in the Netherlands.(40)

Those patients with a failure of infection treatment had a significantly higher ASA score preoperatively as compared to the patients with a successful treatment. This difference is similar to findings in the literature on the infection treatment of hip and knee prosthesis infections.(22,23) No firm conclusion can be drawn due to of lack of statistical power.

The present study has several limitations. The study design is retrospective, and although the number of 48 patients was adequate as compared to other studies in literature, there were only 6/58 failures of treatment. The heterogeneity of patient and operation-related characteristics (time to infection treatment, indication of primary surgery, number of fused levels) in this study makes it hard to interpret outcome. A comparison to literature is even more difficult because of differences in treatment, definitions for outcome, patient characteristics, differences in surgical indications, and prevalence of microorganisms. Another limitation was that the functional outcome was assessed by retrospective analysis of the files at the outpatient clinic.

All currently available clinical evidence regarding the treatment of postoperative infections after instrumented spinal surgery is based on uncontrolled retrospective studies. It is hard to conduct randomized controlled trials, as it would the cooperation of many centres in this field would be required due to the low infection rates and heterogeneity of patient populations.

A valuable alternative for future research would be setting up national and international registries to compare data of diagnosis, operations, comorbidity, and treatment of the infection and outcome variables in large patient populations. Although of lower internal validity as compared to RCT's, evidence of high external validity could be obtained in this way as the included patients would genuinely reflect daily clinical practice.

Conclusion and Clinical Relevance

Debridement and retention of instrumentation in combination with systemic antibiotics and the addition of local antibiotics (gentamicin impregnated PMMA beads or fleeces) results in successful treatment for SSI and non-union after instrumented spinal fusion.

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External validation of a prediction model for surgical site infection after thoracolumbar spine surgery in a Western European cohort

DMC Janssen
SM Kuijk
B d'Aumerie
P Willems

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Chapter V

External validation of a prediction model for surgical site infection after thoracolumbar spine surgery in a Western European cohort

Daniël M. C. Janssen, Sander M. J. van Kuijk, Boudewijn B. d'Aumerie and Paul C. Willems
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Abstract

Background. A prediction model for surgical site infection (SSI) after spine surgery was developed in 2014 by Lee et al. This model was developed to compute an individual estimate of the probability of SSI after spine surgery based on the patient's comorbidity profile and invasiveness of surgery. Before any prediction model can be validly implemented in daily medical practice, it should be externally validated to assess how the prediction model performs in patients sampled independently from the derivation cohort.

Methods. We included 898 consecutive patients who underwent instrumented thoracolumbar spine surgery. To quantify overall performance using Nagelkerke's R^2 statistic, the discriminative ability was quantified as the area under the receiver operating characteristic curve (AUC). We computed the calibration slope of the calibration plot, to judge prediction accuracy.

Results. Sixty patients developed an SSI. The overall performance of the prediction model in our population was poor: Nagelkerke's R^2 was 0.01. The AUC was 0.61 (95% confidence interval (CI) 0.54–0.68). The estimated slope of the calibration plot was 0.52.

Conclusions. The previously published prediction model showed poor performance in our academic external validation cohort. To predict SSI after instrumented thoracolumbar spine surgery for the present population, a better fitting prediction model should be developed.

Introduction

Surgical site infection (SSI) after spinal fusion can have devastating consequences and morbidity that may yield substantial physical limitations with a distinct decrease in quality of life and overall increased health care costs.(1) SSIs can be difficult both to diagnose and to treat. One or more operative debridements combined with prolonged antibiotic treatment may be necessary to eradicate the infection.(1–4)

In spine surgery, a relatively high incidence of SSIs of up to 12% is observed, depending on diagnosis, surgical approach, the use of spinal instrumentation, and the complexity of the procedure.(5–8) Prior research identified several factors associated with an increased risk of SSI: advanced age, obesity, diabetes, smoking, malnutrition, and prolonged duration of surgery.(5,6,9–11) Most of these risk factors are quantified as relative risk or odds ratio. These values are difficult to use in clinical workup before operation to estimate the risk for postoperative SSI and personalize decision-making on individual patient characteristics.

A prediction model is an appropriate tool for shared decision-making during workup to evaluate the individual risk of SSI after spinal surgery and possibly to prevent SSI and its devastating consequences by taking measures before and during surgery.(1) Lee et al. developed a prediction model for SSI after spine surgery that was derived from a surgical spine register of the USA (the Spine End Results Registry). This model was developed to compute an individual estimate of the probability of SSI after spine surgery based on the patient's comorbidity profile and invasiveness of surgery.(11)

A prediction model is most valuable when it is generally applicable. However, before any prediction model can be validly implemented in daily medical practice, it should be externally validated to assess how the prediction model performs in patients sampled independently from the derivation cohort. To the best of our knowledge, the prediction model of Lee et al. has never been externally validated. The aim of the present study was to externally validate the prediction model by Lee et al. in a Western European cohort of patients who received instrumented thoracolumbar spine surgery.

Methods

Study population

For the external validation, we used the data from a prospective cohort of patients > 18 years who underwent instrumented spine surgery from January 1999 up to January 2016 in the Maastricht University Medical Centre.

All operations were performed by three experienced orthopedic surgeons specialized in spine surgery. In some cases, neurosurgeons participated in the operation. All patients underwent an instrumented posterior (posterolateral or interbody) spinal fusion of the thoracolumbar spine with or without an additional procedure (anterior fusion or release, spinal decompression, removal of instrumentation, tumor resection or (partial) corpectomy).

Patients were followed for a minimum of 1.5 year after the index operation to monitor all complications and outcomes of the procedure. All complications, extensive demographics, comorbidity, and surgical details were recorded by collecting data out of all electronic and paper records of the patients. For the preexisting medical comorbidities that were used in the prediction model of Lee et al. (congestive heart failure, diabetes, rheumatoid arthritis), we used the following definition:

Congestive heart failure—a proven decrease of ejection fraction of the heart on ultrasonography and all conditions that decrease the ejection fraction of the heart, including myocardial infarction, angina pectoris, and mitral valve disease in medical history

Diabetes mellitus—insulin-dependent and insulin-independent diabetes mellitus

Rheumatoid arthritis—rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis that had been officially diagnosed by a rheumatologist

We calculated the surgical invasiveness index (SII), as used by Lee et al. for all patients. This index is a validated instrument with a range from 0 to 48 points and contains the sum of six weighted surgical components: number of levels anterior decompressed, anterior fused, anterior instrumented, posterior decompressed, posterior fused, and posterior instrumented. The weight for each component represents the number of vertebral levels at which each respective component has been performed.(12)
The primary outcome of interest was SSI. The diagnosis of surgical site infection in our patient cohort was based on the CDC (Centre for Disease Control and prevention) criteria (13) and the Dutch national PREZIES (*prevention of hospital infections through surveillance*) network.(14) An SSI was considered to be deep if it presented at the site of the operation with involvement of the subfascial tissues. This definition is independent of return to the operating room for irrigation and debridement, in contrast to the definition of SSI used by Lee et al. who defined SSI as an infection requiring return to the operating room. We included all deep infections, even those we did not treat with a re-operation because of terminal illness. All patients had an outpatient appointment at 1 year after the index operation to be registered as "SSI" or "No SSI."

Statistical analysis
For predictor variables that were incomplete, we used stochastic regression imputation. This ensures all observed data can be used for the analysis, preventing a potentially considerable loss of statistical precision. We used predictive mean matching to draw the values to be imputed.

Prediction model
The prediction model of Lee et al. was based on the data of the Spine End Results Registry (SERR). This is a prospectively collected registry for all surgical spine patients at the University of Washington and Harborview Medical Center who underwent surgery from January 1, 2003, to December 31, 2004. This cohort included 1745 patients. One thousand five hundred thirty-two patients were included and were followed for adverse events. Seven hundred thirty-eight (48%) patients consented to provide detailed questionnaires of their risk factors. In 794 (52%) patients, some information about their risk factors, such as smoking status and alcohol use, were missing, as the data for these patients were found either by notification from hospital staff or by medical record review.
The prediction model consisted of seven predictor variables, i.e., body mass index (BMI) classified as normal ($18.5 \leq BMI < 25.0$), underweight ($BMI < 18.5$), overweight ($25.0 \leq BMI < 30.0$), and obese ($BMI \geq 30$) (in the original article, it was not clear whether a BMI of 30.0 would classify as overweight or obese, so we included it in the obese range), diagnosis group (degenerative, trauma, or other), SII score, congestive heart failure (yes or no), diabetes (yes or no), rheumatoid arthritis (yes or no), and age.
In order to derive the prediction formula, we needed regression coefficients, including the intercept. These parameters were not published in the manuscript nor could they be retrieved from the website, or from the authors. Therefore, we took the natural logarithm of the odds ratios presented in the manuscript. These can be used to compute a risk score that ranks patients according to their risk but that does not yield the probability of an SSI. In addition, we used our own cohort to estimate the intercept so that the average predicted probability is exactly the same as the frequency of SSI. After obtaining all regression coefficients, including the intercept, we computed each individual's probability of an SSI using the standard logistic regression formula.

Prediction model performance
We quantified the external validity of the prediction model by computing measures of overall performance, discriminative ability, and calibration. To quantify overall performance, we computed Nagelkerke's R^2 statistic.

Nagelkerke's R^2 is a pseudo-R^2 measure for binary outcomes.
The prediction models' discriminative ability was quantified as the area under the receiver operating characteristic (ROC) curve (AUC). It can be interpreted as the proportion of randomly drawn pairs in which the one developing an SSI has a higher predicted probability than the individual not developing an SSI. It can range between
0.5 and 1.0. The higher, the better the prediction model's discriminative ability. As a sensitivity analysis, we computed the AUC on our sample after excluding deep infections that we did not treat with a re-operation as they would not have been regarded as events according to the definition in the study by Lee et al.
Calibration refers to the agreement between predicted and observed probabilities. We visually inspected the calibration plot to assess whether the prediction model over- or underestimates actual risk for certain risk-based subgroups and computed the calibration slope which ideally should be 1.

Results

The cohort was comprised of a total of 949 patients. Fifty-one patients were excluded: 9 patients were diagnosed before the index operation with an infection after previous back surgery and 42 patients were excluded because there is too little information to be imputed. We included a total of 898 participants for the external validation, of whom 60 (6.7%) were subsequently diagnosed with an SSI, including two deep infections not treated with a re-operation because of terminal illness. Table 1 shows baseline characteristics of all patients included in the study. The predictor variable with the highest number of missing values in our dataset before imputation was BMI (52 missing, or 5.7%). All other predictor
variables were completely observed. After imputation, all records could be used for the analysis.
The back-transforming of the odds ratios published by Lee et al. and the estimation of the intercept based on the present cohort yielded the following formula for the prediction of the probability of an SSI after spinal surgery:
Probability of SSI after spinal surgery = $1/(1 + e^{-LP})$, in which LP = − 3.73 + 1.12*CHF + 0.74*diabetes + 0.70* rheumatoid arthritis + 0.06*SII + 0.002*age + 0.48*trauma − 0.09*other + 0.79*underweight − 0.14*overweight + 0.34* obese.
For example, the probability to develop an SSI after spinal surgery for a 65-year-old overweight male, who has no comorbidities, who will be operated upon due to trauma, and who has an SII score of 10:
LP = − 3.73 + 1.12*0 + 0.74*0 + 0.70*0 + 0.06*10 + 0.002* 65 + 0.48*1 − 0.09*0 + 0.79*0 − 0.14*1 + 0.34*0 = − 2.66.
Hence, the probability of SSI after spinal surgery = $1/(1 + e^{+2.56}) = 0.065 = 6.5\%$.

Prediction model performance

This model was subsequently externally validated. The overall performance was poor: Nagelkerke's R^2 was only 0.01, indicating poor predictive strength. The AUC of the model by Lee et al. applied to our cohort was 0.61 (95% confidence interval (CI) 0.54–0.68), indicating only mediocre discriminative ability (see Fig. 1). Only two patients had a deep infection but were not subsequently re-operated because of terminal illness. In the sensitivity analysis in which we excluded them from the analysis, the AUC did not differ substantially; the AUC was 0.62 (95% CI, 0.55–0.69).
The calibration plot is shown in Fig. 2. The risks of patients at high risk (say, 20% or higher) are on average severely overestimated, as indicated by the fact that the curve lies far beneath the 45° line of perfect calibration. For example, of all patients who had an estimated probability of SSI of about 30%, only 10% actually developed SSI. The estimated slope of the calibration plot was 0.52 compared to an ideal value of 1.

Discussion

We externally validated a previously published prediction model for SSI after spine surgery after back-transforming the published ORs and estimating an intercept specific for our site. The prediction model performed poorly on overall fit, discriminative ability, and calibration. Often, previously developed models perform worse than expected on future patients, especially on patients from different settings. One explanation could be that there is a significant difference in the rate of SSI between our cohort (6.7%) and the cohort of Lee et al. (4.3%), which may have been caused by a difference in patient population.

Table 1 Baseline characteristics of all patients included in the study

Variable	All patients (898)	No SSI (838)	SSI (60)	Lee et al. (1532)
Age	52.2 (SD 16.1)	51.9 (SD 16.0)	56.9 (SD 16.5)	49.5
Gender	M 48.9%; F 51.1%	M 48.6%; F 51.4%	M 53.3%; F 46.7%	M 57%; F 43%
BMI	26.1 (SD 4.7)	26.0 (SD 4.5)	27.9 (SD 5.9)	27.7
ASA	1: 310 (34.5%)	1: 295 (35.2%)	1: 15 (25%)	
	2: 435 (48.4%)	2: 416 (49.6%)	2: 19 (31.7%)	
	3: 150 (16.7%)	3: 125 (14.9%)	3: 25 (41.7%)	
	4: 3 (0.3%)	4: 2 (0.2%)	4: 1 (1.7%)	
Diagnosis*	Trauma 199 (22.1%) De novo degenerative scoliosis 54 (6.0%) Adult spinal deformity 59 (6.5%) Degenerative spinal cord compression disorder 379 (42.1%) Malignancy 42 (4.7%) Failed back surgery 96 (10.7%) One- or two-level degenerative disorder of the spine 61 (6.8%) Spondylodiscitis 8 (0.9%)	Trauma 181 (21.6%) De novo degenerative scoliosis 51 (6.1%) Adult spinal deformity 58 (6.9%) Degenerative spinal cord compression disorder 358 (42.7%) Malignancy 35 (4.2%) Failed back surgery 90 (10.7%) One- or two-level degenerative disorder of the spine 58 (6.9%) Spondylodiscitis 7 (0.8%)	Trauma 18 (30.0%) De novo degenerative scoliosis 3 (5.0%) Adult spinal deformity 1 (1.7%) Degenerative spinal cord compression disorder 21 (35.0%) Malignancy 7 (11.7%) Failed back surgery 6 (10.0%) One- or two-level degenerative disorder of the spine 3 (5.0%) Spondylodiscitis 1 (1.7%)	Trauma 24.3% Degenerative 64.7%
SI score	10.3 (SD 5.9)	10.3 (SD 6.0)	10.1 (SD 5.1)	Mean 8.5
CHF	49 (5.5%)	44 (5.3%)	5 (8.3%)	
Diabetes	73 (8.2%)	66 (7.9%)	7 (11.6%)	
RA	20 (2.2%)	17 (2.0%)	3 (5.0%)	
Previous operation	253 (28.2%)	234 (27.9%)	19 (31.7%)	
Blood loss	1124 mL (SD 1201 mL)	1113 mL (SD 1211 mL)	1276 mL (SD 1044 mL)	
Surgical time	248 min (SD 100 min)	247 min (SD 99 min)	264 min (SD 123 min)	
Cage	42.0%	42.7%	32.7%	
Number of levels fused	3.2 (SD 2.9)	3.2 (SD 2.9)	3.3 (SD 2.5)	
Dural tear	91 (10.1%)	82 (9.8%)	9 (15.0%)	
Combined anterior approach Posterior approach	2.8% 97.2%	2.8% 97.2%	3.4% 96.6%	22.8% 58.7%
Smoking	285 (31.7%)	265 (31.6%)	20 (33.4%)	
Alcohol	334 (37.2%)	305 (36.4%)	29 (40.0%)	
Transfusion	281 (32.9%)	257 (32.2%)	24 (42.9%)	
Using NSAIDs post-OK	433 (48.2%)	398 (47.5%)	35 (58.3%)	
Using NSAID pre-OK	225 (25.1%)	205 (24.5%)	20 (33.3%)	
Amount of transfusion	279 mL (SD 675 mL)	273 mL (SD 682 mL)	367 mL (572 mL)	
Timing AB prophylaxis before surgery	37 min (SD 20 min)	37 min (SD 19 min)	42 min (SD 22 min)	
Mean FiO_2 during surgery	48.9 (SD 12)	48.8 (SD 12)	49.6 (SD 14.4)	

*Degenerative spinal cord compression disorder = spondylolisthesis, spinal stenosis, HNP; De novo degenerative scoliosis = degenerative scoliosis, junctional kyphosis; Adult spinal deformity = kyphosis, juvenile scoliosis, adolescent scoliosis, neuromuscular scoliosis, idiopathic scoliosis; One- or two-level degenerative disorder of the spine = degenerative discopathy, spondylosis, facetarthrosis, adjacent segment degeneration; Fracture = fracture with and without myelum compression; Failed back surgery = failed previous total disc replacement, pseudoarthrosis, failed previous laminectomy, failed previous posterior fusion, failed previous discectomy, failed previous anterior fusion, hardware failure

In contrast to the cohort of Lee et al., we solely included “instrumented” spinal procedures that are known to have a higher infection rate, as seen in the literature.(15) Lee et al. included patients of the Spine End Results Registry (SERR). In this database also, patients without instrumentation were included.(16) The average SI score in our sample was 1.8 points higher compared to the sample of Lee et al. Probably our procedures were more invasive because we solely included “instrumented” procedures and more long-trajectory fusion procedures (e.g., scoliosis). Cizik et al. concluded that surgical invasiveness is the strongest risk factor for SSI after spine surgery, even after adjusting for medical comorbidities, age, and other known risk factors.(16)

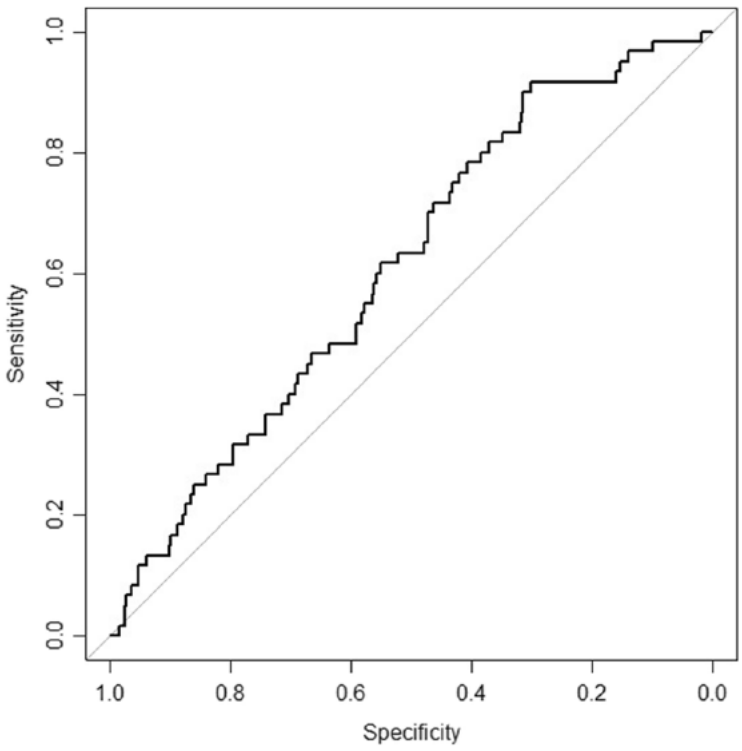

Fig.1 *ROC curve of the prediction model by Lee et al. used to predict SSI*

Lee et al. included a higher percentage of men (57%) than we did in our population (49%). It has been reported that female sex is a predictor of surgical site infection after spine surgery.(17,18) The mean age was approximately the same (49.5 vs. 52.2 years; SD 16.1) between the two populations just as the mean body mass index (27.7 vs. 26.1, SD 4.7). Also, the diagnosis for the index operation is more or less the same. 54.9% in our population had a degenerative condition for treatment (de novo degenerative scoliosis, degenerative spinal cord compression disorder, or one- or two-level degenerative lumbar disc disease) followed by 22.1% trauma, as compared to 64.7 and 24.3% of the population of Lee et al., respectively.

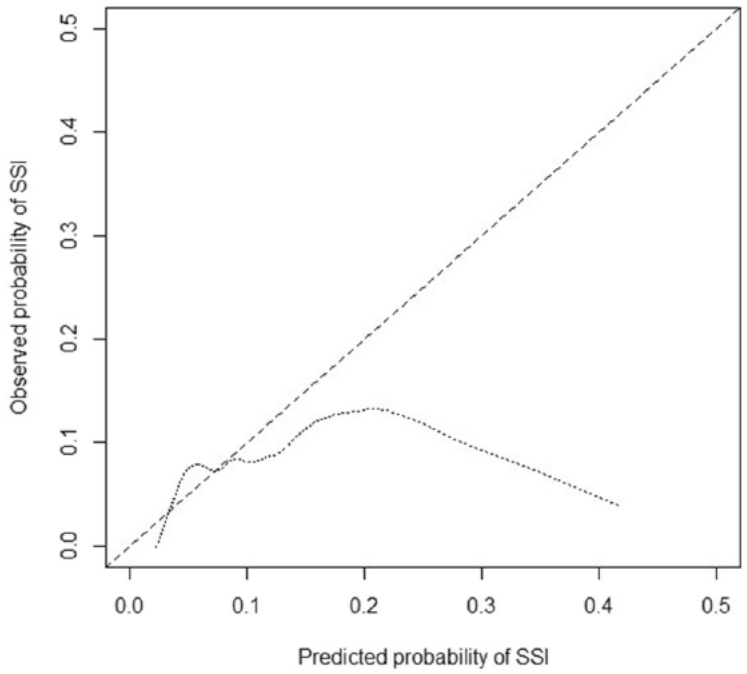

Fig.2 *Calibration plot of the prediction model by Lee et al. used to predict SSI*

All operations were performed using a posterior approach and in 2.8% combined with an anterior approach. This is in contrast to the population of Lee et al., where in 58.7% a posterior approach was used and in 22.8% a combined approach.

In both studies, there is the possibility of underdiagnosis of surgical site infection because of patients that may have been treated elsewhere for SSI without recording in the database. In our study, this would have been only possible in cases with an SSI more than 1 year after the index operation, because we registered the infection status of all patients at 1 year follow-up on the outpatient clinic.

A limitation of this external validation is the potential lack of similarity of definitions of predictor variables. Despite several mail attempts by our study group, the authors of the prediction model were not able to inform us about their methods. In addition, the incidence of preexisting medical comorbidities as used in the prediction model of Lee et al. (congestive heart failure, rheumatoid arthritis, and diabetes) could not be compared because these were not further specified in the article.

A second limitation is the sample size of our cohort. Even though the absolute size is quite large, the number of events (SSI) is only 60. A study suggests using at least 100 events and 100 non-events for an external validation study.(19) Therefore, our results may be less precise.

In prior research, more risk factors were identified to increase the risk of SSI after spine surgery than used in the prediction model of Lee et al. In our opinion, some of these factors would be important to include in a model for SSI following (instrumented) spinal surgery of the thoracolumbar spine: smoking, alcohol use, and previous spine surgery.(5,6,20) These factors are important in shared decision-making and communication with patients undergoing spinal surgery because some of these factors, such as smoking behavior, can be adapted during workup.

Conclusion

The model presented by Lee et al. shows poor predictive performance in our cohort of Western European patients undergoing instrumented spinal surgery. For valid and accurate prediction of SSI after instrumented spine surgery in an academic center, a better prediction model should be developed, preferably with more, and better-defined risk factors earlier described in literature for a patient population that is better comparable with the population in our academic spine center. After the development of such a prediction model, this should also be externally validated in similar populations to use it as a broad and more general model. A valuable tool for validations of new models could be high-volume national and international registry data to compare factors such as diagnosis, operations, comorbidity, and incidence of infection in large patient populations, because of the low incidence of SSI in spine surgery.

Abbreviations

AUC: Area under the receiver operating characteristic curve; BMI: Body mass index; CDC: Centre for disease control and prevention; CHF: Congestive heart failure; LP: Linear prediction; METC: Medical ethics committee; OR: Odds ratio; PREZIES: Prevention of hospital infections through surveillance; ROC: Receiver operating characteristic; SD: Standard deviation; SERR: The Spine End Results Registry; SII: Surgical invasiveness index; SSI: Surgical site infection;

USA: United States of America; WMO: Medical Research Involving Human Subjects Act

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A prediction model of surgical site infection after instrumented thoracolumbar spine surgery in adults

DMC Janssen
SM Kuijk
B d'Aumerie
P Willems

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Chapter VI

A prediction model of surgical site infection after instrumented thoracolumbar spine surgery in adults

Daniël M. C. Janssen, Sander M. J. van Kuijk, Boudewijn d'Aumerie, Paul Willems
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Abstract

Purpose. The aim of this study was to develop and internally validate a multivariable model for accurate prediction of surgical site infection (SSI) after instrumented spine surgery using a large cohort of a Western European academic center.

Method. Data of potential predictor variables were collected in 898 adult patients who underwent instrumented posterior fusion of the thoracolumbar spine. We used logistic regression analysis to develop the prediction model for SSI. The ability to discriminate between those who developed SSI and those who did not was quantified as the area under the receiver operating characteristic curve (AUC). Model calibration was evaluated by visual inspection of the calibration plot and by computing the Hosmer and Lemeshow goodness-of-fit test.

Results. *S*ixty patients (6.7%) were diagnosed with an SSI. After backward stepwise elimination of predictor variables, we formulated a model in which an individual's risk of an SSI can be computed. Age, body mass index, ASA score, degenerative or revision surgery and NSAID use appeared to be independent predictor variables for the risk of SSI. The AUC was
0.72 (95% CI 0.65–0.79), indicating reasonable discriminative ability.

Conclusions. We developed and internally validated a prediction model for SSI after instrumented thoracolumbar spine surgery using predictor variables of standard clinical practice that showed reasonable discriminative ability and calibration. Identification of patients at risk for SSI allows for individualized patient risk assessment with better patient-specific counseling and may accelerate the implementation of multi-disciplinary strategies for reduction of SSI.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-018-05877-z) contains supplementary material, which is available to authorized users.

Introduction

Surgical site infection (SSI) is one of the most serious complications after spine surgery with potentially devastating consequences such as failure of fixation, osteomyelitis, pseudarthrosis, increased length of hospital stay, mortality, unfavorable surgical outcome and associated health care costs.(1–5) Within the field of orthopedic surgery, a relatively high incidence of SSIs is observed after spine surgery: up to 12% depending on diagnosis, surgical approach, use of spinal instrumentation and the complexity of the procedure.(6–8) SSIs can be both difficult to diagnose—as there is no pathognomonic sign or symptom to accurately indicate its presence—and difficult to treat. One or more operative debridements combined with prolonged antibiotic treatment may be necessary to treat the infection.(1,9,10) With the rise in prevalence of antibiotic-resistant organisms, the treatment of SSI has become even more difficult, and therefore, the prevention of SSI is a matter of utmost importance.(11)

Prior research has identified several factors associated with an increased risk of SSI after spine surgery, e.g., advanced age, revision surgery, obesity, diabetes, smoking, high amount of intraoperative blood loss and prolonged duration of surgery.(6,7,12–14) These risk factors are usually reported as relative risks (RR) or odds ratios (OR). However, these RRs and ORs are measures of association and are not sufficient to estimate an individual's personal risk of SSI given a combination of these factors.

Combining risk factors into a prediction model is an appropriate tool to be used for preoperative patient counseling when evaluating the individual risk of SSI after spinal surgery. Estimating an individual's risk of SSI may help identify high risk patients, thus optimizing patient selection with possible prevention of the devastating consequences and associated outcomes of an SSI after surgery.(1)

Lee et al. developed a prediction model for SSI after spine surgery based on the patient's comorbidity profile and invasiveness of surgery by using a prospectively collected registry for all surgical spine patients at University of Washington and Harborview Medical Center consisting of 1532 patients having instrumented and non-instrumented spinal surgery.(12) However, external validation of the prediction model showed poor predictive performance in a large cohort of patients undergoing instrumented thoracolumbar spine surgery in an academic spine setting.(15)

The aim of this study was to develop and internally validate a multivariable prediction model for accurate prediction of SSI after instrumented spine surgery using a large cohort of a Western European academic center.

Methods

Patient population

This was a retrospective cohort study of all instrumented spinal surgery procedures of the thoracic, lumbar and thoraco-lumbar spine that have been performed in adult patients (≥ 18 year) in an academic referral center for spinal pathology from January 1, 1999, up to January 1, 2016. Patients diagnosed with an infection after instrumented spinal surgery elsewhere were excluded as well as patients for whom the medical files for at least up to 1 year after surgery were not available.

All operations were performed by 3 experienced orthopedic surgeons specialized in spine surgery. In select cases when neurological decompression was needed, neurosurgeons participated in the operation. All patients underwent an instrumented posterior (posterolateral or interbody) spinal fusion of the thoracic, lumbar and thoracolumbar spine, with or without an additional procedure (anterior fusion or release, spinal decompression, the removal of instrumentation, tumor resection or corpectomy/osteotomy). Patients were followed for a minimum of 1 year after the index operation to monitor all complications and incidences of revision surgery. All complications, extensive demographics, comorbidity and surgical details were recorded by collecting data from all available electronic and paper records of the patients. The primary outcome of

interest was the occurrence of SSI. The diagnosis of SSI was based on the CDC criteria (Centre for Disease Control and prevention) (16) and the Dutch national PREZIES network (*prevention of hospital infections through surveillance*).(17) An SSI was considered to be deep if it presented at the site of the operation with involvement of the subfascial tissues.

Predictor variables

An often-used rule of thumb states that at least 10 events (i.e., occurrences of SSI) are needed per predictor variable that is tested in the prediction model development step.(18) When more predictor variables are added to the model, the probability of overfitting (i.e., the model predicts exceedingly worse for patients not comprised in the derivation cohort) increases. As a result, we needed to perform a pre-selection of all baseline characteristics of those that we thought would be most likely to result in an accurate prediction model. The pre-selection was based on what was already known from other studies, the distribution of the predictor in our sample, and experience in our own hospital. Using this method, we were able to reduce the initial set of potential predictor variables to 8, i.e., age, body mass index (BMI: kg/m^2), smoking status, diagnosis, revision surgery, ASA (American Society of Anesthesiologists) physical status, surgical invasiveness index (SII) (19) and the use of non-steroidal anti-inflammatory drugs (NSAIDs) preoperatively. Smoking status was dichotomized into currently smoking yes or no, independent of the volume and tobacco product used. All passive smokers and ex-smokers were regarded as non-smoker. ASA physical status, a classification to assess the fitness of the patient before surgery, was coded according to the five-category physical status classification system of the American Society of Anesthesiologists in 1963 (1 = healthy person, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe systemic disease that is a constant threat to life, 5 = a moribund person who is not expected to survive without the operation).(20) The surgical invasiveness index is a validated instrument with a range from 0 to 48 points, containing the sum of the following six weighted surgical components: the number of levels anterior decompressed, the number of levels anterior fused, the number of levels anterior instrumented, the number of levels posterior decompressed, the number of levels posterior fused and the number of levels and posterior instrumented. The weight of each component represents the number of vertebral levels at which each respective component has been performed.(19) A higher score means higher invasiveness. For example, in an L4–L5 posterior fusion and decompression with the use of an intervertebral cage, and posterior instrumentation, the score would be 9 (anterior fusion = 2, anterior instrumentation = 2, posterior decompression = 1, posterior fusion = 2, posterior instrumentation = 2).

Diagnosis of the included patients was divided into 4 sub-groups, i.e., one- or two-level degenerative disorders (with or without neurologic compromise), failed back syndrome (patients that had already undergone previous spine surgery on the same level), trauma (unstable vertebral fractures with or without neurological compression) and other (adult spinal deformity, spinal metastases/malignancy, spondylodiscitis). Nonsteroidal anti-inflammatory drugs use was defined as the daily use of NSAIDs before surgery for more than 1 week and still in use at the time of surgery.

Model development

Incomplete patient records were imputed using stochastic regression imputation, to prevent a potentially considerable loss of statistical precision and to decrease the probability of biased results when compared to using only complete patient records (Table 1). We used predictive mean matching to generate the imputed values. After imputation, we included all potential predictor variables in a logistic regression analysis. Using stepwise backward elimination on the hypothesized predictor variables, we excluded nonsignificant predictors from this category to arrive at a more parsimonious model. As suggested by prediction modeling guidelines, we used a less strict alpha for eliminating variables from the model to prevent too early deletion of potentially

important predictor variables.(21) We chose to use an alpha of 0.10 compared to the conventional 0.05.
For continuous variables, the association is assumed to be linear. Nonlinear effects were visualized using plots and formally tested using restricted cubic splines, a regression technique that can be used to test for deviations from linearity.(21) In case of significant evidence of a nonlinear relation, the continuous variable was categorized into clinically meaningful categories.
The model's performance was quantified using measures of discriminative ability and measures of calibration. We assessed the model's ability to discriminate between those who developed SSI and those who did not by computing the area under the receiver operating characteristic (ROC) curve (AUC). This AUC can range from 0.5 (no discriminative ability) to 1.0 (perfect discriminative ability). Model calibration (i.e., agreement between predicted and observed probabilities) was evaluated by visual inspection of the calibration plot and by computing the Hosmer and Lemeshow goodness-of-fit test (HL test). A significant HL test indicates evidence against good model fit.

Internal validation
We internally validated the initial prediction model using standard bootstrapping techniques. Using results from the bootstrap procedure, we penalized the model's regression coefficients, so future predictions will be less extreme (to counter the effect of overfitting) by multiplying them with a shrinkage factor, and re-estimating the model intercept. Also, we computed the estimated optimism in the AUC. This is a measure of the likely difference in AUC when the model is applied to future patients. All analyses were performed using R version 3.3.3.

Results
A total of 898 participants were available for the development of the prediction model. Sixty (6.7%) were subsequently diagnosed with SSI.
Table 1 shows a summary of baseline variables including all potential predictor variables of the whole cohort and separately for those who developed SSI and those who did not.
The restricted cubic spline regression revealed evidence of a U-shaped association between BMI and SSI instead of a linear one. Therefore, we categorized BMI into three clinically relevant subgroups: normal weight (BMI up to 25), overweight (BMI between 25 and 30) and obese (BMI over 30). The backward stepwise elimination yielded the following predictor variables: age, BMI categories, ASA physical status, degenerative or revision (versus trauma and other) and the use of NSAIDs. All other potential predictor variables were eliminated from the model because their *p* value was higher than 0.10.
The ROC curve of the prediction model is shown in Fig. 1. The AUC was 0.72 (95% confidence interval (CI) 0.65–0.79), indicating reasonable discriminative ability. The calibration plot is shown in Fig. 2. It shows the model is well calibrated for the whole range of predicted probabilities, as it lies close to the 45-degree line of perfect fit.

Table 1 *Baseline characteristics of all patients included in the study*

Variable	All patients (898)	No SSI (838)	SSI (60)	*p* value
Age	52.2 (SD 16.1)	51.9 (SD 16.0)	56.9 (SD 16.5)	0.100
Gender	M 48.9%; F 51.1%	M 48.6%; F 51.4%	M 53.3%; F 46.7%	0.476
BMI	26.1 (SD 4.7)	26.0 (SD 4.5)	27.9 (SD 5.9)	0.003
ASA				0.004
1	310 (34.5%)	295 (35.2%)	15 (25%)	
2	435 (48.4%)	416 (49.6%)	19 (31.7%)	
3	150 (16.7%)	125 (14.9%)	25 (41.7%)	
4	3 (0.3%)	2 (0.2%)	1 (1.7%)	
Diagnosis*				0.717
Trauma	199 (22.1%)	181 (21.6%)	18 (30.0%)	
Adult spinal deformity	113 (12.5%)	109 (13.0%)	4 (6.7%)	
One- or two-level degenerative spinal disorder with neurologic compromise	379 (42.1%)	364 (43.4%)	20 (33.3%)	
Malignancy	42 (4.7%)	35 (4.2%)	7 (11.7%)	
Failed back surgery syndrome	96 (10.7%)	91 (10.8%)	6 (10.0%)	
One- or two-level degenerative spinal disorder without neurologic compromise	61 (6.8%)	60 (7.1%)	3 (5.0%)	
Spondylodiscitis	8 (0.9%)	7 (0.8%)	1 (1.7%)	
SI score	10.3 (SD 5.9)	10.3 (SD 6.0)	10.1 (SD 5.1)	0.259
Cardiac pathology	49 (5.5%)	44 (5.3%)	5 (8.3%)	0.310
Diabetes	73 (8.2%)	66 (7.9%)	7 (11.6%)	0.323
Rheumatic disease	20 (2.2%)	17 (2.0%)	3 (5.0%)	0.132
Previous operation	253 (28.2%)	234 (27.9%)	19 (31.7%)	0.533
Blood loss	1124 mL (SD 1201 mL)	1113 mL (SD 1211 mL)	1276 mL (SD 1044 mL)	0.868
Surgical time	248 min (SD 100 min)	247 min (SD 99 min)	264 min (SD 123 min)	0.871
Cage	378 (42.0%)	358 (42.7%)	20 (32.7%)	0.154
Number of levels fused	3.2 (SD 2.9)	3.2 (SD 2.9)	3.3 (SD 2.5)	0.190
Dural tear	91 (10.1%)	82 (9.8%)	9 (15.0%)	0.197
Combined anterior approach	25 (2.8%)	23 (2.8%)	2 (3.4%)	0.788
Smoking	285 (31.7%)	265 (31.6%)	20 (33.4%)	0.738
Alcohol	334 (37.2%)	305 (36.4%)	29 (40.0%)	0.268
Blood transfusion	281 (32.9%)	257 (32.2%)	24 (42.9%)	0.101
Amount of transfusion	279 mL (SD 675 mL)	273 mL (SD 682 mL)	367 mL (572 mL)	0.638
Using NSAIDs preoperative	442 (48.2%)	406 (48.4%)	36 (60.0%)	0.084
Timing antibiotics	37 min (SD 20 min)	37 min (SD 19 min)	42 min (SD 22 min)	0.375
Mean fraction of inspired oxygen	48.9 (SD 12)	48.8 (SD 12)	49.6 (SD 14.4)	0.175

*Trauma = fracture with or without neurologic symptoms

Adult spinal deformity = kyphosis, juvenile scoliosis, adolescent scoliosis, neuromuscular scoliosis, idiopathic scoliosis, degenerative scoliosis, junctional kyphosis

One- or two-level degenerative spinal disorder with neurologic compromise = spondylolisthesis, spinale stenose, HNP

Failed back surgery syndrome = pseudarthrosis, failed previous total disk replacement, previous laminectomy, discectomy, posterior fusion/anterior fusion, or hardware failure

One- or two-level degenerative spinal disorder without neurologic compromise = degenerative disk disease, spondylosis, facet arthritis, adjacent segment degeneration

The internal validation step yielded a shrinkage factor of 0.87. All regression coefficients were multiplied by this factor to shrink them closer to 0 to produce less extreme predictions for future patients, to counteract the effect of model overfitting.

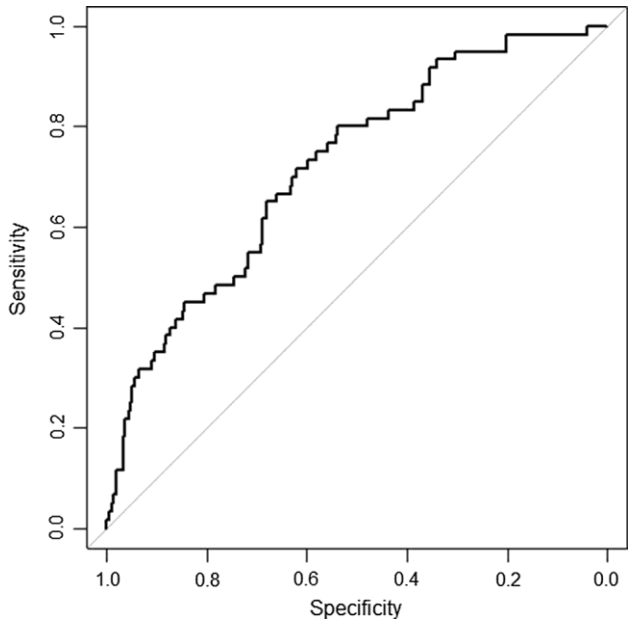

Fig. 1 *Receiver operating characteristic curve of the prediction model for surgical site infection*

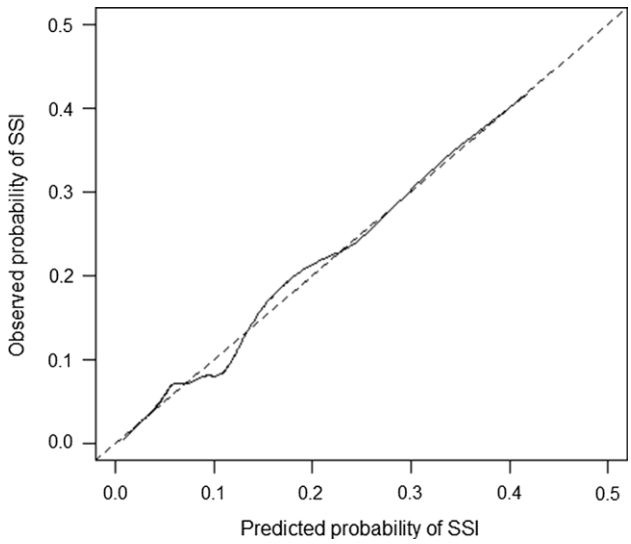

Fig. 2 *Calibration plot of the prediction model for surgical site infection*

Prediction model

Table 2 shows the coefficients of the resulting prediction model. The way to calculate an individual's risk of an SSI is shown in detail in Table 1.

Table 2 Prediction model for the occurrence of surgical site infection

Variable	Regression coefficient	Odds ratio (95% CI)	*p* value	Shrunk regression coefficient[a]
Intercept	−4.388	–	–	−4.159
Age	0.016	1.01 (1.00–1.04)	0.100	0.014
BMI 25–30	−0.721	0.49 (0.23–0.97)	0.048	−0.631
Obese	0.584	1.79 (0.93–3.42)	0.078	0.510
ASA score	0.600	1.82 (1.22–2.74)	0.004	0.524
Degenerative or revision	−0.661	0.52 (0.29–0.92)	0.023	−0.578
NSAID use	0.259	1.30 (0.95–1.73)	0.084	0.226

[a]After adjustment for overfitting by shrinkage (shrinkage factor = 0.87). The intercept was subsequently re-estimated

Discussion

This manuscript presents an internally validated predictive model to estimate the risk of SSI after instrumented thoracolumbar spinal fusion. In the literature, risk factors are generally reported as relative risks or odds ratios. Although these measures of association are important in understanding what contributes to an individual's probability of an SSI, they are difficult to translate into a tool for decision making and cannot be used to calculate an individual's probability of an SSI. The prediction model presented in this manuscript can be used to predict an individual risk (as a proportion or percentage) for SSI after instrumented spinal fusion.

This model may be helpful in the clinical setting to identify patients at high risk of SSI, optimizing patient selection and possibly prevent devastating consequences and associated outcomes of an SSI after surgery by extra preventive measures such as prolonged antibiotic prophylaxis or optimalization of nutritional status.

To our knowledge, this is the first prediction model for SSI after instrumented spine surgery procedures. The model has an AUC of 0.72 (95% CI 0.65–0.79). This is considered to be moderate and is comparable to prediction models from other clinical disciplines with an AUC range from 0.54 to 0.73.(22,23) Bear in mind that the model is used for prediction of future events, compared to diagnostic models that estimate the probability of the presence or absence of an outcome in the present time. Arguably, predicting the future is much more complex, like Niels Bohr said: "prediction is very difficult, especially about future."

Lee et al. presented a model for SSI in 2014 based on 1532 patients.(12) In the model of Lee et al., all spine surgery procedures were included, whereas in our model only instrumented procedures were included. A second difference between the two models was the definition of SSI. Lee et al. defined SSI as an infection requiring return to the operating room for irrigation and debridement without a clear difference between superficial and deep infection. Our definition of SSI was based on the CDC criteria and the Dutch national PREZIES network including only deep infections independent of return to the operating room.

One of the limitations of the model that we developed is the number of patients in our cohort. Although we used a large cohort consisting of 898 patients, more patients (and subsequently more cases of SSI) would have given us the opportunity to study even more potential predictor variables. Remarkably, some potential predictor variables that were important in other studies, like smoking and surgical invasiveness index, were

not selected in our modeling procedure.(6,13) This could be due to a lack of statistical power, also related to the number of patients in our cohort. Other risk factors described in the literature with a very low incidence in our cohort, like Parkinson's disease and paraplegia, were not selected.(24)

Some other associations between predictor variables and SSI were unexpected (25,26): We did not observe a linear association between BMI and the log-odds of an SSI. Overweight patients with a BMI between 25 and 30 were more protected for SSI compared to normal weight (BMI 20-25), but obese and morbidly obese patients with a BMI of more than 30 were more prone to an SSI after instrumented spine surgery. In most literature, only (morbid) obesity (BMI > 30) is described as risk factor for SSI after spine surgery although overweight patients with a BMI less than 30 were not described as a risk factor.(7,13,27) A hypothesis for mild overweight as a protective factor could be that these patients have more soft tissue covering of the instrumentation after an instrumented spinal procedure.
Most predictive variables were in agreement with the literature. Age, ASA score, and diagnosis were significant risk factors for SSI in our model. In the previous literature, patients with comorbid medical conditions were found to be significantly associated with SSI.(7,28,29) Trauma, adult spinal deformity with long segment procedures, spondylodiscitis and malignancy had a higher risk for SSI than degenerative or failed back surgery syndrome.(6,30–33) Also older age had an increased risk of postoperative spinal infection.(13,34)
Although this model can be of great benefit when considering risk assessment, it would be most valuable if it was generalizable to future patients and patients from different hospitals. Hence, it should be externally validated to assess how the prediction model performs in patients sampled independently from the derivation cohort.

Conclusion

We presented an internally validated predictive model for SSI after instrumented thoracolumbar spine surgery. This tool can be of substantial value in the preoperative counseling of patients for shared surgical decision making and ultimately improve safety in spine surgery. Identification of patients at risk for postoperative infection allows for individualized patient risk assessment with better patient-specific counseling and may accelerate the implementation of multidisciplinary strategies for the reduction of SSIs.

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Antibiotic release from PMMA spacers and PMMA beads measured with ELISA: assessment of in vitro samples and drain fluid samples of patients

DMC Janssen
P Willems
J Geurts
CJJ Arts

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Chapter VII

Antibiotic release from PMMA spacers and PMMA beads measured with ELISA: assessment of in vitro samples and drain fluid samples of patients.

Janssen Daniël MC, Paul Willems, Geurts Jan, Arts Chris JJ
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Abstract

Background: For prosthetic joint infections, antibiotic loaded poly methyl methacrylate (PMMA) spacer or beads can be used to release high concentrations of antibiotics locally at the infection site, while minimizing systemic toxicity.

Objectives: The aim of this study is to determine *in vitro* and *in vivo* pharmacokinetic release profile of antibiotics from PMMA spacers and PMMA beads.

Methods: For the *in vitro* experiment the PMMA spacers or beads were submerged in phosphate-buffered saline and gentamicin concentrations were determined from collected specimen at several times points, measured with ELISA.
To assess the *in vivo* antibiotic release profile of different spacers, wound drainage fluid samples were collected after implantation of a spacer over a period of maximum 14 days.

Results: After 48 hours the burst gentamicin concentration elution was 9,862 ± 1,782 ng/ml (mean ± SD) from spacers vs. 38,394 ± 7,071 ng/ml (mean ± SD) for beads. Over 35 days, spacers had eluted a cumulative mean concentration of 13,812 ± 3,548 ng/ml vs. 55,048 ± 12,006 ng/ml for beads (P<0.001).
Clinical samples of patients with a Vancogenx® spacer showed higher gentamicin release than Refobacin™ spacers (P<0.001).

Conclusion: This is the first study that measured the release data of local antibiotics with ELISA. Compare to spacers, the exact release values of gentamicin from PMMA beads are more than 10 times higher and reached a maximum much later than spacers. This makes the use of PMMA beads more preferable to use for treatment of the infection itself.

Level of evidence: Level II

Introduction

The primary objective of treatment of prosthetic joint infections (PJIs) is the eradication of infection while maintaining a correctly functioning implant. Debridement, antibiotics and implant retention (DAIR) and one- or more-stage exchange procedures are treatment strategies that are selected according to type of infection (acute or low grade), cultures, condition of the soft tissue and comorbidities of the patient. Success rates depend on the delay between primary implantation and infection treatment and on the sensitivity of the causative microorganism.(1–4) In chronic low-grade infections or a loose implant, a one-stage or two-stage exchange procedure with an antibiotic loaded poly methyl methacrylate (PMMA) spacer is indicated, with success rates between 67-95%.(5–7)

As an added local treatment of the infection site, antibiotic loaded PMMA has the advantage of releasing high concentrations of antibiotics locally at the infection site, while minimizing systemic toxicity.(8) Antibiotics released from the bone cement ideally provide concentrations far above the minimal inhibitory concentrations (MIC) value of the causative pathogen.(9) Antibiotic release from antibiotic loaded PMMA is based on reciprocal diffusion and is divided into two different phases. In the first 24-96 hours hour there is dissolution of a high local concentration of antibiotics from the surface of the PMMA into the body fluid, called burst release. This is followed by 4-30 days sustained release of antibiotics where water-soluble antibiotics diffuse out of the PMMA into the body fluid. During the second phase of sustained release, a lower concentration of antibiotics is achieved but for a longer duration.(10) The duration and concentration of antibiotic release is depending on the type of antibiotics and release capacities of the PMMA. Increasing the surface area by increasing the surface roughness and porosity will result in an increasing of dissolution of antibiotics from the surface into the body fluid.(11,12) Also adding polymeric fillers and highly water-soluble substances increase the release capacities.(10,12)

Antibiotic loaded PMMA-bead chains can be implanted surgically in a debrided bone (osteomyelitis or after removing an implant) or at the implant site if the implant remains in situ. After 2-4 weeks the bead chains should be removed surgically.(1,13) The introduction of spacers improved the technical possibilities for a two-stage approach of prosthetic joint infection.(14–17) Compared to PMMA beads, spacers facilitate largely the reimplantation, because of maintaining length of soft tissues, reducing the risk of dislocation and facilitate non-weight bearing mobility. They allow for greater patient comfort during the intervening period between removal and reimplantation. Disadvantage of spacers compared to antibiotic loaded PMMA beads is an inferior maximum antibiotic concentration, due to a largely reduced surface, resulting shorter period of antibiotic release above MIC.(18–23)

There is some contradiction in literature about the *in vivo* antibiotic concentration and duration of antibiotic release of this local antibiotic loaded PMMA applications. In some studies the authors suggest that antibiotic elution levels of spacers often fall below the MIC value needed to inhibit bacterial growth after several days (24,25), while other studies concluded that this drop below the MIC value occurred only after more than 3 months.(26–28) When antibiotic levels drop below the MIC value, they can develop antibiotic resistance.(29,30)

Most studies that analysed elution of antibiotics from PMMA materials *in vitro* or *in vivo* used high-pressure liquid chromatography (HPLC) or fluorescent polarizing immunoassay to determine antibiotic concentration. Disadvantage of both methods is that they are heavily influenced due to protein content in samples.(31) Because wound secretion is protein-rich, chromatographic or fluorescent methods are less appropriate to define antibiotic concentrations in such samples. With enzyme-linked immunosorbent assays (ELISA) it is possible to detect gentamicin and vancomycin at low concentrations in protein-rich specimen, such as wound secretion fluids.(31)

The aim of this study is to determine a 35 days pharmacokinetic release profile of gentamicin from femoral PMMA StageOne select spacers and prefabricated commercially gentamicin loaded PMMA beads in an *in vitro* test environment using an ELISA detection methodology. Secondly, this study assessed maximum 14 days pharmacokinetic release profile of gentamicin and vancomycin from PMMA Stage-One select spacers collected from clinical joint arthroplasty patient drains samples *in vivo* using an ELISA detection methodology. We hypothesized that StageOne select spacers would demonstrate higher and longer lasting pharmacokinetic antibiotic release profiles as reported results of earlier generations.

Materials and methods

StageOne Select hip spacer (Figure 1)

The StageOne Select Hip Cement Spacer system (Zimmer-Biomet, Warsaw, IN, USA) is a single-use silicone mold with a stainless-steel reinforced stem and head intended to be filled with bone cement. Upon curing of the antibiotic loaded cement, the spacer mold creates a temporary cement spacer for patients undergoing a two-stage revision due to infection. The device is intended for use in conjunction with systemic antimicrobial antibiotic therapy (standard treatment approach to an infection). Perceived benefits are an improved function by personalized sizing options and the creation of a greater joint motion. Additionally, and relevant to this in vitro study, the new textured surface is expected to demonstrate an optimized antibiotic elution profile.

In this study, 8 gentamicin-impregnated StageOne™ Select Refobacin® Bone Cement R spacers (Figure 1) were used to determine the pharmacokinetic antibiotic release profile of gentamicin in an *in vitro* setting. Refobacin® Bone Cement R (Biomet, Dordrecht, the Netherlands) was used, which contains a pre-defined concentration of 0.5 g gentamicin per 40 g bone cement. The spacers were made by manually-mixing the liquid (monomer) and powder (polymer) and filling in the silicon stem molds (Size 11 x 200 mm) at atmospheric conditions, according to the manufacturer's guidelines by an experienced orthopaedic surgeon (JG). For the elution study, the spacer was positioned in 1 liter phosphate-buffered saline (PBS).

Figure 1. *Left: The StageOne Select Hip Cement Spacer mold. Right: Visualisation of a complete StageOneTM Select Refobacin® Bone Cement R spacers (Zimmer-Biomet, Warsaw, IN, USA).*

PMMA beads preparation

Beads were hand-made in the lab with the use of prefabricated metal casted, Teflon-coated molds, available from the University of Vermont.(32) These produce chains of 25 beads with a diameter of 6,4 mm, on a metal, non-braided strand of 0.8mm. The production process was conducted at room temperature, in a clean vacuum hooded environment. Using a standard cement mixing system (without application of vacuum), the cement is then injected into each hole in the bead mold, applying gentle pressure. Cement which is expulsed through

adjacent holes is removed by scraping a spatula along the top of the mold. Twenty minutes of setting time are than applied. Beads are subsequently removed from the molds, resulting in a chain of 25 beads. As with the spacers, Refobacin® Bone Cement R was used. For the elution study 20 beads were positioned in a closed 1L bottle with 200 ml PBS.

ELISA methodology

To investigate the pharmacokinetic antibiotic release of antibiotics from PMMA spacers and PMMA beads (*in vitro*) and for the clinical used PMMA spacers and PMMA beads (*in vivo*), an indirect competitive ELISA was performed. (31) This protocol was published earlier by Odekerken et al.(31) Prior to the measurement, each well of the plate was coated with 10 ng gentamicin-bovine serum albumin (BSA, PAA Laboratories, Germany) or 1 µg vancomycin-BSA in coating buffer (50 mm carbonate/bicarbonate buffer; pH 9,6) and incubated overnight at 4°C. The coupled haptens gentamicin-BSA and vancomycin-BSA were generated with the usage of N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC, Sigma Aldrich, USA). After incubation, the wells were washed with wash buffer (0.05% Tween 20 in PBS) and blocked with blocking buffer (5% BSA and 0.05% Tween 20 in PBS) for 1 hour at room temperature. Subsequently, calibration curve samples (range gentamicin: 0–1000 ng/ml and vancomycin: 0–5000 ng/ml) or test samples were added to the blocking buffer. Then, the primary antibody was added and incubated for 1 hour at room temperature. The primary antibodies gentamicin (mouse anti-gentamicin monoclonal antibody, clone 26.16, Abcam/Abnova) and vancomycin (rabbit anti-vancomycin polyclonal antibody, Bioconnect) were diluted 7000x and 5000x in blocking buffer, respectively. Thereafter, the wells were washed and blocked for 1 hour at room temperature. Afterwards, the plate was washed and the secondary antibody was added and incubated for 1 hour at room temperature. The secondary antibodies for gentamicin and vancomycin were diluted 5000x (rabbit anti-mouse peroxidase; RAMPO, Dako, Denmark) and 2000x (swine anti-rabbit peroxidase; SWARPO, Dako, Denmark) in blocking buffer, respectively. After 1 hour, the plate was washed and the substrate 3,3',5,5'-Tetramethylbenzidine (TMB, Sigma Aldrich, USA) was added to each well. The colouring reaction was stopped with stop buffer (3M sulfuric acid, H2SO4) when the absorbance of the blank well was between 0.45 and 0.55, measured at 650 nm (MultiSkan FC, Thermo Scientific). Finally, the absorbance was measured at 450 nm and the values were presented in log-log scale. The concentrations were calculated by performing regression analysis in the VBA Analysis ToolPak (Microsoft Office 365, Excel) and graphs were generated using GraphPad Prism (version 6.01). All wash steps were performed 3 times and all incubation steps were performed during continuous shaking.

Experimental timelines in vitro

For the *in vitro* experiment PMMA spacers or PMMA beads (20 beads-chain) were fully submerged in PBS, after preparation, and incubated at room temperature under continuous shaking, Mot 15/min. The same PBS was used during the experiment without changing. At several times points (0h, 1h, 2h, 5h, 17h, 1d, 2d, 4d, 7d, 10d, 14d, 18d, 21d, 28d and 35d), 1 ml was collected of each sample and stored at -20°C until analysis. During analysis absolute gentamicin concentrations were determined at each time point without taken weight of the spacer or the beads and loss of fluid volume into account. Secondly, we also calculated the concentration of the gentamicin release, as measured with ELISA, multiplied by the volume in which the spacer or beads were placed. This analysis takes into account the volume that is taken for the measurement and the volume that has evaporated during the experimental timeline. This weight of total gentamicin release per time point is divided by the weight of the spacer or beads-chain.

Clinical PMMA samples

To assess the *in vivo* antibiotic release profile of different bone cement types, the pharmacokinetic antibiotic release of gentamicin was quantified in all clinical samples, whereas the antibiotic release of vancomycin was only determined in two patients. Patients 1 to 4 and 7 to 9 underwent a hip replacement and patient 5 and 6 underwent a knee replacement. The wound drainage fluid samples were collected every 24 hours after implantation of a spacer over a period of maximum 14 days. The samples were analysed by performing the ELISA and the given values were not standardized to the original volume of wound drainage fluid.

The *in vivo* clinical samples were wound drainage fluids of joint arthroplasty patients (n=9), which were treated with either Refobacin™ spacer, PALACOS® R+G spacer, Vancogenx® spacer or gentamicin-impregnated spacer (Tecres®). During the operation of extraction the prosthesis and implantation of the spacer the surgeon left a drain in the joint space, coming out of the skin near the incision and connected with a closed wound unit. The first days after operation there was no suction of the drains until the wound drainage fluids was lower than 50cc per 24 hours, then suction was used to collect wound fluid for a longer time. Every 24 hours wound drainage fluid were collected from the container and stored at -20°C until analysis. The pharmacokinetic antibiotic release was followed for a maximum of 14 days.

T-test was used for statistical analyses between spacer and cement group. SPSS (version 17.0) was used for all statistical calculations.

This study was approved by METC Maastricht University: 14-4-110. All patients provided informed consent prior to participation in the clinical study

Results

Quantification of the pharmacokinetic antibiotic release

PMMA spacers in vitro

The absolute gentamicin concentration from the StageOne Select hip PMMA spacers during 35 days without adjusting for weight and fluid loss is displayed in figure 2. In the first 48 hours of submersion, the burst absolute gentamicin elution was high and an antibiotic concentration of 9,862 ± 1,782 ng/ml (mean ± SD) was measured at 48 hours. At day 7, the spacers had eluted a cumulative mean concentration of 12,958 ± 1,644 ng/ml. Over the following days, the gentamicin elution gradually decreased and stabilized over time. Eventually, the spacers showed a total elution concentration of 13,812 ± 3,548 ng/ml over a period of 35 days. When adjusting for the volume that is taken for the measurement and the spacer weight, the weight (mg/g) of total gentamicin release per time point can be calculated (Figure 3).

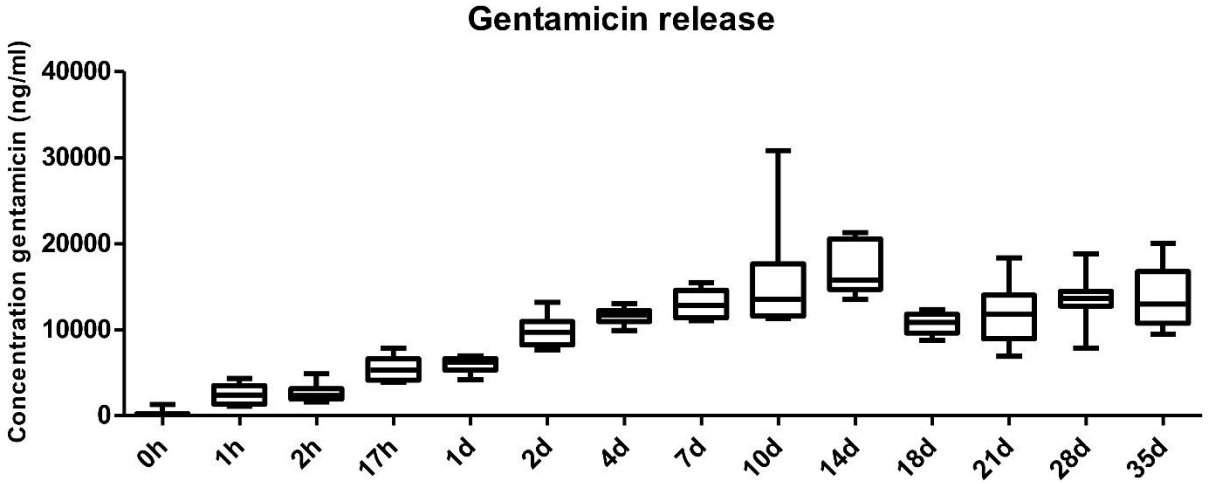

Figure 2. *Gentamicin elution profile (ng/ml) from StageOne Select spacers (n=8). The total absolute gentamicin concentration elution of 9,862 ± 1,782ng/ml after 48 hours. Total cumulative gentamicin elution of 12,958 ± 1,644 ng/ml after 7 days. Total cumulative gentamicin elution of 13,812 ± 3,548 ng/ml over a period of 35 days. Results are presented as the mean ± SD (n=8).*

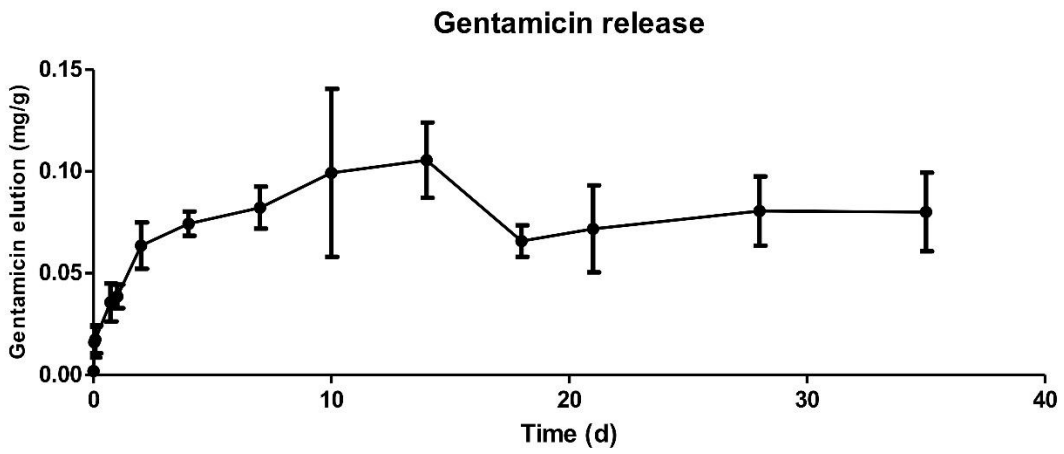

Figure 3. *Total gentamicin release (µg/g) per time point from StageOne Select spacers (n=8) adjusting for the volume that is taken for the measurement and the spacer weight.*

PMMA beads in vitro

The absolute gentamicin concentration from the PMMA beads during 35 days without adjusting for weight is displayed in figure 4. During the first 48 hours of submersion, it turned out that the burst absolute gentamicin elution was high and an antibiotic concentration of 38,394 ± 7,071 ng/ml (mean ± SD) was measured from the beads in the first 48 hours, which is significant more than the burst gentamicin elution form spacers (P<0.001). At day 7, the beads had eluted a cumulative mean concentration of 47,446 ± 10,526 ng/ml. Over the following days, the gentamicin elution gradually decreased and stabilized over time. Eventually, the beads showed a total elution concentration of 55,048 ± 12,006 ng/ml over a period of 35 days. When adjusting for the volume that is taken for the measurement and the bead weight, the weight (mg/g) of total gentamicin release per time point was calculated (Figure 5).

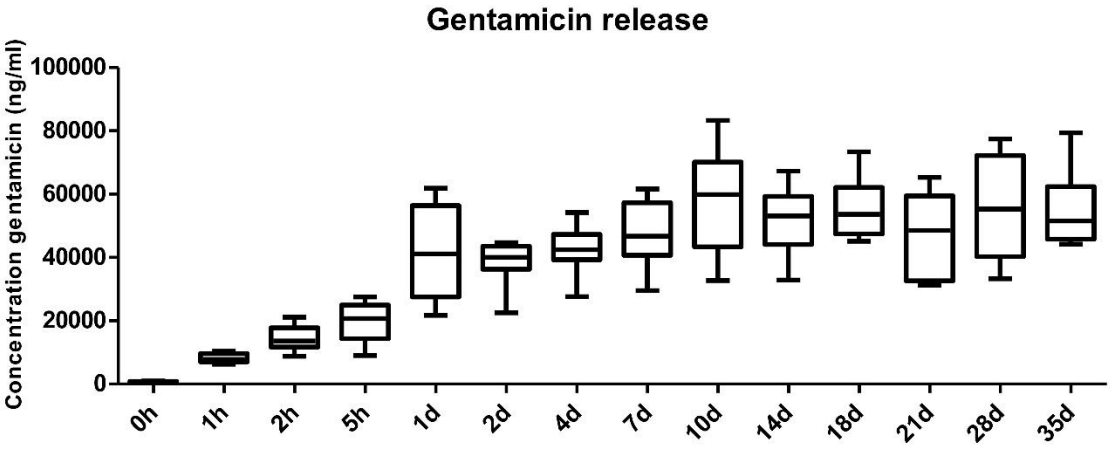

Figure 4. *Gentamicin elution profile (ng/ml) from PMMA beads (n=8). The total absolute gentamicin concentration elution of 38,394 ± 7,071 ng/ml after 48 hours. Total cumulative gentamicin elution of 47,446 ± 10,526 ng/ml after 7 days. Total cumulative gentamicin elution of 55,048 ± 12,006 ng/ml over a period of 35 days. Results are presented as the mean ± SD (n=8).*

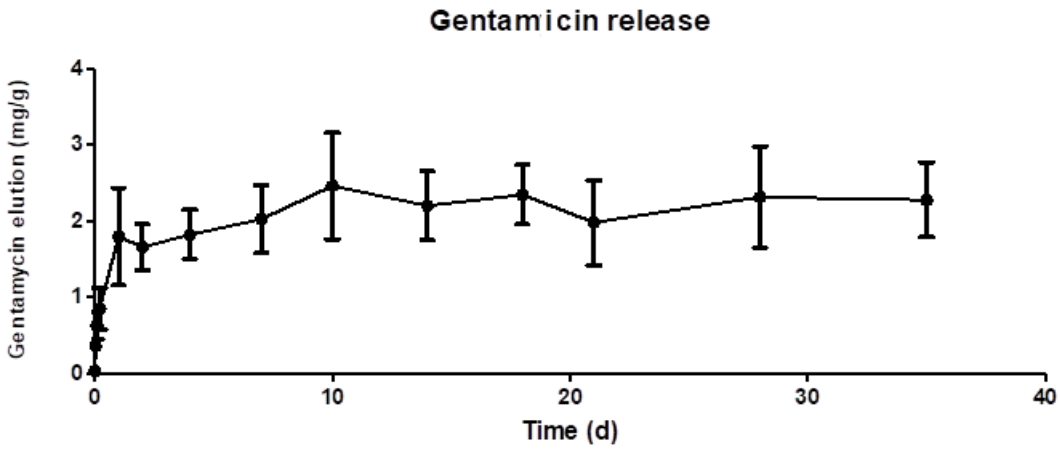

Figure 5. *Total gentamicin release (mg/ml) per time point from PMMA beads (n=8) adjusting for the volume that is taken for the measurement and the beads weight.*

Clinical samples

In table 1 and figure 6 and 7, it is shown that patient 1, 2 and 3 with gentamicin containing Refobacin™ spacer eluted a total amount of 38.64 µg, 26.27 µg and 41.52 µg, over a period of 9, 6 and 13 days respectively. Patient 1 and 2 showed an increase of about 19 µg, while the amount of gentamicin of patient 3 was 8.44 µg after 24 hours of implantation. Patient 4 was treated with gentamicin-impregnated PALACOS® R+G spacer and released an amount of 35.27 µg after 11 days. The amount of gentamicin was not directly increased after implantation. The gentamicin-impregnated spacer (Tecres®) in patient 5, 6 and 7 eluted a total amount of 67.17 µg, 55.89 µg and 35.07 µg, over a period of 14, 6 and 5 days respectively. The spacers of patient 5 and 6 eluted a higher total amount of gentamicin after 3 days compared to other gentamicin containing spacers.
Patient 8 and 9 were treated with gentamicin – and vancomycin-impregnated spacers (Vancogenx®) and eluted a cumulative amount of gentamicin of 85.07 µg (7 days) and 101.35 µg (5 days), respectively. The

elution of gentamicin was reduced but constant in all patients after 3 days. Furthermore, patient 8 and 9 showed a total cumulative vancomycin elution of 56.69 µg and 45.12 µg for 7 and 5 days, respectively (table 2, figure 6 and 8). The vancomycin release from the dual-antibiotic spacer was not stabilized yet.

Time (days)	Patient 1 (hip)	Patient 2 (hip)	Patient 3 (hip)	Patient 4 (hip)	Patient 5 (knee)	Patient 6 (knee)	Patient 7 (hip)	Patient 8 (hip)	Patient 9 (hip)
	Refobacin™	Refobacin™	Refobacin™	PALACOS®R+G	Tecres®	Tecres®	Tecres®	Vancogenx®	Vancogenx®
1	20,96	17,78	8,44	2,45	*	29,73	14,65	24,05	29,24
2	37,84	23,5	13,55	3,3	*	40,22	25,72	51,35	63,54
3	*	24,03	23,49	21,78	16,37	44,33	30,64	66,04	88
4	*	24,98	28,44	24,08	41,74	51,88	32,75	74,83	97,32
5	38,41	25,71	32,08	27,08	46,52	*	35,07	79,43	101,35
6	38,58	26,27	34,56	28,93	*	55,89		82,22	
7	38,6		36,07	*	55,56			85,07	
8	38,62		40,25	29,6	59,22				
9	38,64		40,73	30,27	61,99				
10			*	31,7	63,52				
11			*	32,03	63,95				
12			41,04		65,73				
13			41,52		66,4				
14					67,14				

Table 1. *Cumulative amount of gentamicin (µg) in 9 patients. Patient 1-4 & 7-9 hip spacer. Patients 5 and 6 knee spacer. *=Drainage fluid not usable for measurement*

Time (days)	Patient 8	Patient 9
1	18,87	9,95
2	27,81	23,43
3	34,94	33,97
4	41,71	40,48
5	48,38	45,12
6	54,35	
7	56,39	

Table 2. *Cumulative amount of vancomycin (µg) in patient 8 and 9.*

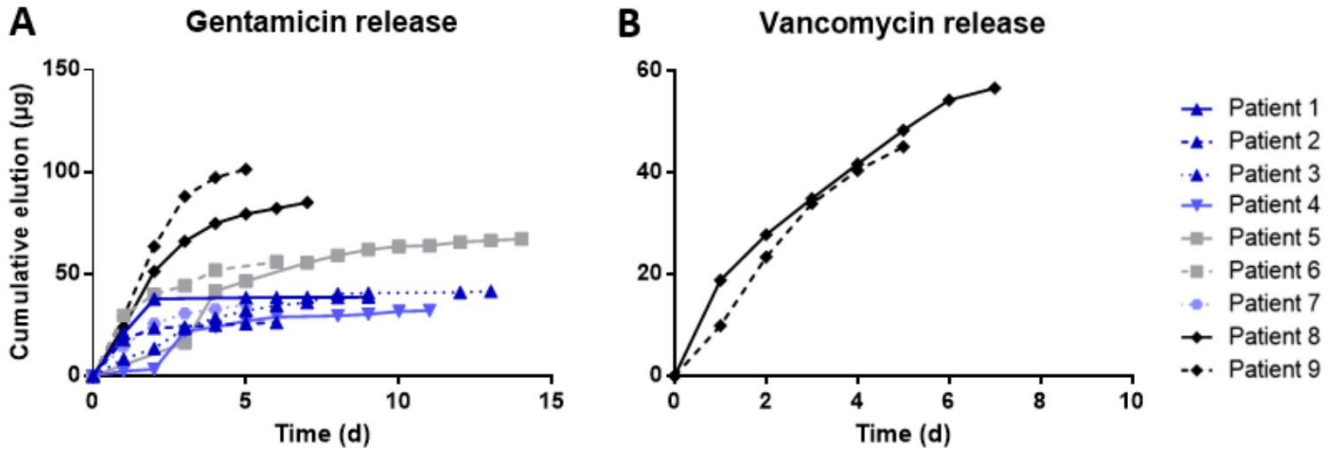

Figure 6. *Cumulative gentamicin and vancomycin elution profiles. (A) Total cumulative gentamicin elution of 38.64 µg (patient 1), 26.27 µg (patient 2), 41.52 µg (patient 3), 35.27 µg (patient 4), 67.17 µg (patient 5), 55.89 µg (patient 6), 35.07 µg (patient 7), 85.07 µg (patient 8) and 101.35 µg (patient 9). (B) Total cumulative vancomycin elution of 56.69 µg (patient 8) and 45.12 µg (patient 9).*

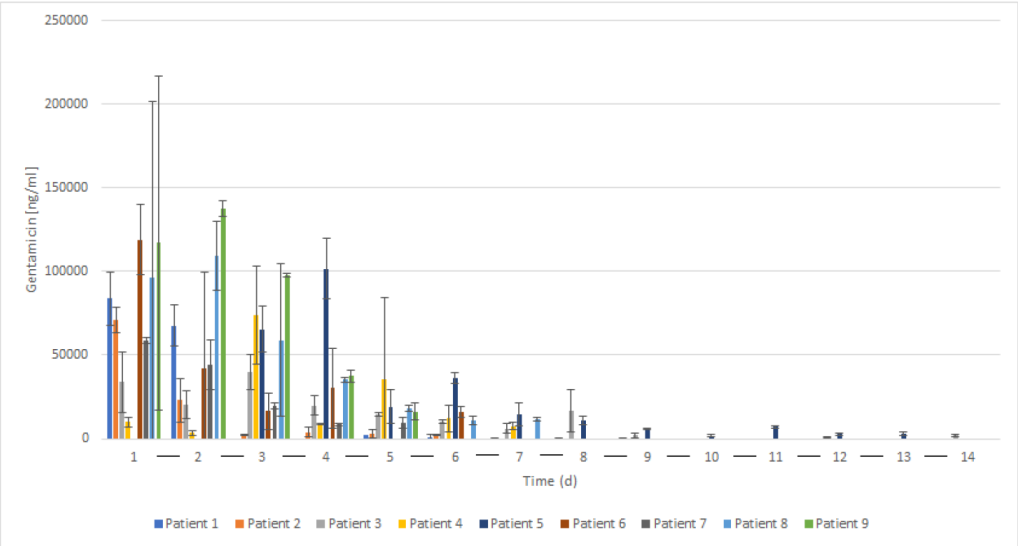

Figure 7. *Results of measured gentamicin concentration in 9 patients over a period of 14 days.*

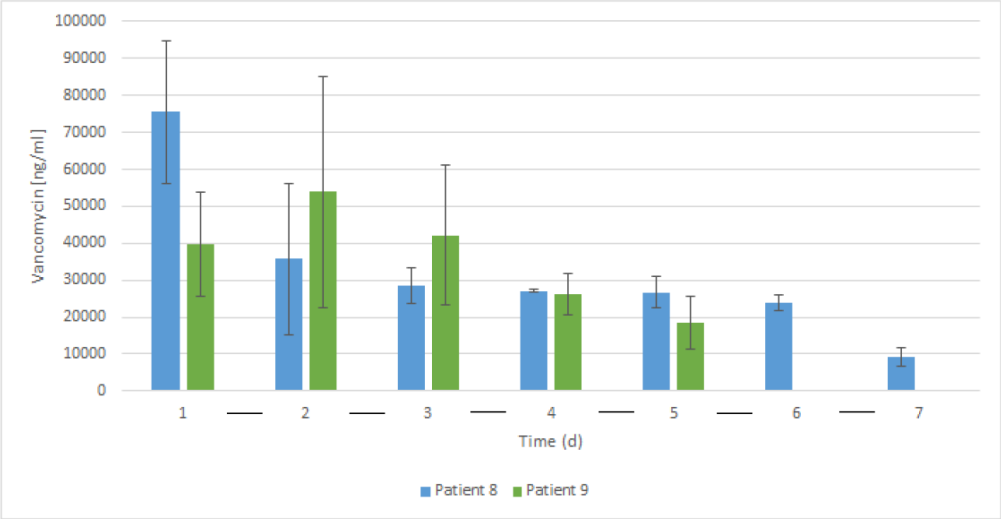

Figure 8. *Results of measured vancomycin concentration in patient 8 and 9 of 7 days.*

Discussion

Since the introduction, the antibiotic pharmacokinetic profile properties of spacers have been under continuous development. First-generation spacers were monoblock, hand-molded spacers that could incorporate selective antibiotics. Different studies showed that the antibiotic release concentrations of these spacers exceeded MICs of most pathogens in the first few hours to days of implantation.(33,34) However, since there is a limited number of studies of prolonged antibiotic release concentrations, the current evidence regarding these concentrations should be interpreted with care. Recent 3rd generation antibiotic-impregnated PMMA spacer are able to provide a high concentration of antibiotics at the site of infections.(35) In recent years material technology developments have offered several options for an improved and prolonged antibiotic pharmacokinetic released profile. It was the aim of this study to assess whether 3rd generation antibiotic-impregnated PMMA spacer StageOne select would exhibit superior antibiotic release profiles as compared to first generation PMMA spacers. This study concluded that in a 35-day *in vitro* test environment StageOne select antibiotic-impregnated PMMA spacers do yield a higher and prolonged antibiotic release kinetic compared to earlier generation antibiotic-impregnated PMMA cement spacer, however it did not reach

statistical significance. When compared to the same volume of PMMA beads, the spacers vastly underperformed in antibiotic pharmacokinetic released profile.

There are a lot of different methods to measure the release of antibiotics of antibiotic carriers, with different outcome and without a universally accepted protocol. Because this is the first study that measured the release data of local antibiotics with ELISA, the results are very difficult to compare with current literature. This makes it impossible to compare exact release data, but release pharmacokinetic release profiles are more or less comparable. In this study the release of gentamicin from spacers reached a maximum in de first 24 hours. After 24 hours of a gentamicin burst release there is plateau phase with a significant lower prolonged release of gentamicin. This is comparable to other literature with spacers.(23,24,33) Compared to the release of gentamicin, the exact release of vancomycin from spacers in the clinical samples of this study is much lower in µg. In contrast to the gentamicin release, the pharmacokinetic release profiles of vancomycin showed a gradual increase of vancomycin release, without a plateau phase in the first 5 to 7 days. Other literature also showed lower exact release values and a longer burst release of vancomycin compare to gentamicin.(33) The release of gentamicin from PMMA beads is reaching a plateau phase much later compare to spacers, after 10-14 days. The exact release values are also more than 10 times higher compare to the release of gentamicin of spacers which is also comparable to current literature.(23)

Spacers are mainly useful to maintain a better joint function in long interval infection treatment, but compare to gentamicin beads, less preferable to use for treatment of the infection itself, since they result in lower local gentamicin exudate levels than gentamicin loaded PMMA beads. In long interval two-stage infection treatment the main disadvantage of gentamicin beads is that beads are less comfortable than spacers. And the main disadvantage of gentamicin beads in '*in situ*' treatment is that you need an extra operation to remove the beads. Unfortunately, these two disadvantages make the use of gentamicin beads in infection treatment of prosthesis less attractive in the last decade whereby the advantage of a high local antibiotic concentration and better infection treatment is also lost. For future use, resorbable beads would be the solution to avoid an extra operation for removing the beads and taking advantage of the high antibiotic release.(36,37) For future research these resorbable beads should also be examined for pharmacokinetic release profiles. To take the advantage of the function of the spacer and the high antibiotic concentration of gentamicin loaded PMMA beads it is also possible to combine both local antibiotics, whereby the spacer avoid to use that many beads as possible in a situation without a spacer.(38)

This study has several limitations. First, this study used a standard mixing method that still could have led to variability in PMMA cement porosity and pharmacokinetic release profiles. Due to the experimental setup, we were not able to check this parameter. Despite having high sample numbers and observing consistent trends in our experiment, we did note variability in our data that could be contributed to a PMMA cement porosity variance. The ELISA assessment methodology was successfully employed in both analyzing the in vitro samples and this analysis was also not hampered when analyzing the clinical drain samples. Furthermore, this study was a quantitative study of gentamicin and vancomycin elution only without microbiological study analysis on attained MIC value.

Conclusion

This study is the first that analyses the release profile of local antibiotics, beads and spacers, with ELISA.

The burst gentamicin release of spacers in the first 48 hours was 9,862 ± 1,782 ng/ml (mean ± SD), after which a plateau phase is reached with a significant lower prolonged release of gentamicin. The burst release of PMMA beads was significant higher than spacers, 38,394 ± 7,071 ng/ml (mean ± SD). PMMA beads reaches a plateau phase much later than spacers, after 10-14 days with exact release values more than 10 times higher than PMMA spacers.

Over 35 days, spacers had eluted a cumulative mean concentration of 13,812 ± 3,548 ng/ml vs. 55,048 ± 12,006 ng/ml for beads, $P<0.001$.

Clinical samples of patients with a Vancogenx® spacer showed higher total amount of gentamicin release than Refobacin™ spacers in a 14-day time period.

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Discussion

Chapter VIII

Discussion

The incidence of primary prosthetic joint infection (PJI) ranges between 1-2% in literature, and it may be increasing. Due to this increasing incidence and a higher number of total joint arthroplasty procedures, it has been predicted that infection will become the most frequent mode of failure of total knee and hip arthroplasty.(1–5) The incidence of surgical site infection (SSI) after spinal surgery ranges from 2 to 12% depending on diagnosis, surgical approach, use of spinal instrumentation and the complexity of the procedure.(6,7)
SSI is a devastating complication that leads to prolonged treatment with the need for subsequent reoperations and substantially increased overall health care costs. Moreover, SSI after instrumented orthopaedic procedure is associated with higher rates of morbidity and mortality, and has a negative impact on clinical outcome.(8,9)

In the first part of this thesis the treatment of surgical site infection after total knee and total hip prosthesis, and after instrumented spinal fusion with the use of local antibiotics was described. An analysis of failures of infection treatment including risk factors for failure was listed.

The first aim was to report the results of operative debridement with retention of the prosthesis and local antibiotics in a cohort of 89 patients with postoperative or haematogenous deep infections of stable total hip and total knee implants.
For stable, well-fixed total knee prosthesis treated by debridement and retention of the prosthesis, in combination with systemic and local antibiotics, there was a success rate for infection treatment of 82%. For stable, well fixed hip prosthesis treated by debridement and retention of the prosthesis, in combination with systemic and local antibiotics, there was a success rate of 83%. In our cohort polyethylene components or modular heads were not replaced routinely before 2010. Probably, the success rates would have been higher if this had been done in every patient.(10,11) Nowadays this is the standard procedure in our department and in worldwide literature.

For prosthesis infections of less than 4 weeks after primary implantation we found a risk for failure of 0.2 For a joint age (time after primary implantation of the prosthesis) between 4 and 8 weeks the risk for failure increased gradually and if the infection treatment started more than 8 weeks after the primary implantation the risk for failure became 0.5.

The success rate of in situ treatment of infected well-fixed hip and knee prosthesis of more than 80% is difficult to compare with current literature, because the success rates of in situ treatment vary largely in literature (31%-100%). Because of increasing technical options nowadays for revision surgery, like spacers and other designed revision prosthesis, retention of the implant is controversial, especially for prosthesis infection with a longer interval between the primary implantation and infection treatment.(11–17)

Compared to other studies that analysed debridement, antibiotics and implant retention (DAIR) we had relatively good results in our study with retention of the prosthesis. Even in infections with a postoperative interval of more than 8 weeks, with a risk for failure 0.5 (CI 0.2-0.8).(11,17,18)
In infections with an interval of less than 4 weeks the risk for failure was 0.2 (CI 0.1-0.3) and these results are comparable to cases that were treated by debridement and antibiotics with extraction of the prosthesis.(19)

In the current guidelines for prosthetic joint infections it is recommended to limit the acceptable period of symptoms to a maximum of 3 weeks for a treatment with retention of the prosthesis if the prosthesis is stable, the soft tissues are in good condition, and the causative microorganism susceptible to antibiotics.(20)
In contrast to these recommendations, an increasing number of studies showed also acceptable outcome with retention of the prosthesis after more than 3 weeks.(11,17,18,20,21) . This may have been caused by the fact that in situ treatment has become more successful in recent years, also in longer interval after index surgery, because modular components are exchanged nowadays. Especially if the causative microorganism is highly sensitive for antibiotics.(18)

So, in contrast to the recommendation of earlier guidelines DAIR can be considered a successful treatment in well-fixed implant infections, even if the infection and symptoms are delayed.(17,18) Nevertheless, individual factors should always be taken into account. For instance, in case of DAIR for an infected prosthesis, that the patient should be able to tolerate antibiotic combination regimes, often with rifampicin, for a prolonged duration.(22) In early high suspected prosthesis infection with a negative culture DAIR is also an indicated treatment, without high risk of complications or significant harm to implant failure.(23)

A possible explanation for the good results in our study for DAIR could be the use of local antibiotic carriers in our treatment protocol (gentamicin loaded beads or collagen). These carriers have a high surface area for antibiotic release and therefore achieve a high local antibiotic concentration above the minimal inhibitory concentration (MIC value) of the causative pathogen, without systemic toxic effects.(24)

The second aim of this thesis was to report the results of a two-stage infection treatment and local antibiotics in infected total knee and total hip prosthesis.
We described the results of a two stage treatment of total knee and total hip prosthesis over a period of 24 years with the use of local antibiotics. The failure rate after one single 2-stage infection treatment was 12%. Because stable, well-fixed prosthesis infections were treated with retention of the prosthesis, this cohort was more difficult to treat, because of a longer interval between primary implantation and infection treatment.(25) The more difficult infection selection in this cohort, because of the (relative) contra-indication for treatment with retention of the prosthesis, is likely the reason for the lower success rate.(26) Fifty percent of the failures became free of infection after a second infection treatment. Re-infection after a two-stage infection treatment of a hip or knee arthroplasty is very challenging because of the more difficult-to-treat microorganisms with higher resistance patterns and the more compromised soft tissue coverage. The success rate of this second infection treatment is comparative with rates found in literature,(27) in which a second infection treatment showed a much lower success rate than a primary treatment.(28) 3 out of 120 cases (2.5%) were never infection free and 4 (3.3%) died during infection treatment because of poor health condition with malignancy in 2 cases and, poor health condition caused by the infection.
Because this study described a 24 years period, in the beginning only gentamycin beads were used as local antibiotics without a spacer. Since the application of spacers there were more reimplantations of prosthesis. Although spacers release antibiotics, in our treatment protocol we used spacers mainly to keep enough room between the articulating bones in order to keep soft tissues at length and facilitate reimplantation, as well as to provide better function during the period between extraction and re-implantation of the prosthesis (concept of dead space management).
Besides the high success rate in DAIR infection treatment, with the use of local antibiotics in the two stage exchange infection treatment of hip and knee prosthesis, and in DAIR for instrumented spine infection showed high success rates. Despite these good results the use of gentamicin beads has never been widely used in

prosthetic infections or spine infections. Probably one of the reason for this is that gentamicin beads have never been approved by the FDA in the US.(29)
For local antibiotic treatment gentamicin loaded PMMA beads were used. This consideration is based on release studies, but clinical studies do not show more persistent infections with only the use of spacers compared to gentamycin beads. In fact, a higher hip score, a shorter hospital stay, and better walking capacity in the interim period were associated with the use of spacer prosthesis. Furthermore, a decreased operative time, less blood loss, and a lower transfusion requirement were shown at the time of re-implantation in patients with spacers only.(30)
In literature we found two studies that also described specifically the use of antibiotic loaded beads in two stage revision prosthetic infection treatment. In 2002 Taggart et al. reported the results of 33 arthroplasties (26 hips and 7 knees) which had been performed in a two stage revision procedure implemented by the use of vancomycin impregnated cement beads for infection caused by different organisms. After a mean follow-up of 67 months, 32 patient remained clinically and radiologically free from infection. The authors concluded that vancomycin played a major role in the management of infection after arthroplasties.(31)
Chen et al. demonstrated good results using a protocol of aggressive surgical debridement, local antibiotic-loaded cement beads, combined parenteral and oral antibiotic therapy and reimplantation after normalization of ESR and CRP levels.: forty-six out of forty-eight (96%) hips treated following this protocol and using interim antibiotic-impregnated cement beads were free of recurrent infection, at least according to the clinical examination and laboratory tests at their latest follow up; thirty-five patients (74%) achieved excellent or good results.(32). Despite the lack of comprehensive literature about the use of antibiotic loaded PMMA beads in two stage revision prosthetic infection treatment, the abovementioned studies show good results comparable to our study.

The third aim was to report the results of a treatment protocol including local antibiotics in surgical site infections after instrumented spine surgery.
In the fourth chapter of this thesis we evaluated 58 deep SSIs after instrumented fusions of the thoracolumbar spine managed with a treatment protocol consisting of repetitive surgical debridement, supplemented with local gentamicin releasing carriers and systemic antibiotics, between 1999 and 2016. In case of non-union, the intention of this treatment protocol, was to retain the instrumentation or in case of loosening to restabilise the instrumentation during surgical debridement to provide a stable spine. In case of consolidated fusion the instrumentation was removed during debridement. The outcome measures of interest were eradication of the infection and residual pain or limitations in daily living. 52 of the 58 (89.7%) patients had a successful resolution of infection with a stable spine at the end of treatment without recurrence of infection after a minimum of one year follow-up.
As in prosthesis infections also in infections after instrumented spine surgery gentamicin beads can be used to create a high local gentamicin concentration at the site of the infected implant material
The main difference in spine surgical site infections compared to joint prosthesis infections is the importance of stability to achieve bony union. In SSIs after instrumented spinal fusion, stable instrumentation should be left in situ as long as bony fusion has not occurred yet.
The use of antibiotic loaded beads in instrumented spine infections has been described even less in literature than the use in joint prosthesis infections.(33,34)
If local antibiotic loaded beads are used, patients are required to undergo a minimum of 2 anaesthetic procedures compared to one-stage treatment.

Despite the scarcity in literature concerning the use of gentamicin impregnated beads in infection treatment of orthopaedic implants, we think that gentamycin beads can be especially of use in specific difficult to treat infections with more resistant microorganisms. Moreover, the use of local antibiotics by means of impregnated beads in instrumented spine infections can provide a beneficial effect on the outcome as an additional treatment, because application of alternative local antibiotics, like spacers and bone cement in prosthetic joint infections, is not possible in spinal infections.
Because there are no universally accepted protocols for the treatment of deep surgical site infection after instrumented spine surgery, the results of our study cannot be compared to a sort of gold standard.(35) However, the success rates presented in our study are higher than in most studies.(33–38). Large number controlled research or elaborate well-documented spinal registries would be needed to confirm whether the additional use of gentamicin beads is beneficial in the treatment of SSIs of instrumented spine surgery.

Unfortunately, most literature about treatment of surgical site infections is retrospective in nature, because of the low infection rates and heterogeneity of patient populations. Small sample populations are inadequate for analysing factors that influence treatment outcome and success rate after a spine or prosthesis infection. Moreover, studies are very difficult to compare through differences in treatment protocol, definitions for infection, indications and outcome of treatment, differences in patients characteristics and identified microorganisms. Because of this, it is very hard in practice to conduct randomized controlled trials. An alternative for future research would be national and international registries to compare data of diagnosis, operations, treatment and outcome of infection treatment in large populations.

After instrumented spine surgery, the rate of a surgical infection is relatively high. The availability of an easy-to-use prediction model would be of great help to select those patients that are at highest risk. In prediction research, an important step is to search for existing models and see whether these are applicable in your clinical patient setting.
After thoroughly searching the literature in spine surgery, one prediction model was found that used only few predictors to estimate an individual's probability of a surgical site infection. Lee et al. developed a prediction model for SSI after spine surgery that was derived from a surgical spine register of the USA (The Spine End Result Registry). This model was developed to compute an individual estimate of the probability of SSI after spine surgery based on the patient's comorbidity profile and invasiveness of surgery.(39)

The fourth aim of this thesis was to assess the external validity of this previously published prediction model for surgical site infection after spine surgery in our patient population, a Western European cohort of patients that underwent instrumented thoracolumbar spine surgery in a university hospital.
The prediction model performed poorly on overall fit, discriminative ability, and calibration. This poor performance could be attributed at least in part to a different patient cohort. In our academic Western European cohort only instrumented spinal procedures were included with a higher infection rate, while in the cohort of Lee et al. also non-instrumented procedures were included. As the predictors were estimated based partially on procedures which were not included in our setting, and no predictor variables quantified this difference, model performance decreased substantially compared to the performance in the development sample. As a result, we concluded that in our population this model did not perform sufficiently to be generally used for the prediction of surgical site infection and as this was the only model that had been developed at that time, we decided to develop a model specifically for the population of patients with instrumented spinal procedures.

The fifth aim of this thesis was to develop a prediction model that can be used in daily practice to estimate the risk of an SSI after instrumented spine surgery for an individual patient.
We developed a multivariable prediction model based on easily obtainable predictors that could be used in daily practice: https://www.evidencio.com/validations/show/330. The developed prediction model had an Area Under the Curve (AUC) of 0.72 (95% CI: 0.65 – 0.79), indicating reasonable discriminative ability.
Because a model usually performs much better in the cohort of patients used to develop the model compared to future patients for whom the predicted probability will be calculated, we performed an internal validation. This internal validation yielded an estimate of the performance of the model in future patients, adjusted for the optimism that is present in performance parameters estimated on the development data. Furthermore, the initial prediction model was also adjusted for overfitting, i.e. the fact that, on average, regression coefficients are overestimated and hence, produce too extreme predictions in future patients. We adjusted the model for overfitting by multiplying the regression coefficients by a *shrinkage factor*, a constant between 0 and 1, to prevent future predictions from being too extreme. For this development and internal validation, we used a large cohort of a Western European academic center. The model included the following predictor variables: age, BMI categories, ASA physical status, degenerative or revision (versus trauma and other), and the use of NSAID's. All other potential predictor variables were eliminated from the model as they were not significantly contributing ($p>0.10$).
This model may be helpful in the clinical preoperative setting to identify patients at high risk of SSI, optimizing patient selection and possibly prevent devastating consequences and associated outcomes of an SSI after surgery. Identification of patients at risk for postoperative infection allows for individualized patient risk assessment with better patient-specific counseling, and may accelerate the implementation of multi-disciplinary strategies for the reduction of SSIs.
However, before recommending widespread use in clinical practice, the model will need to be externally validated. Only if external validation shows sufficient performance for the intended goal in other clinical settings, the model can be implemented.
After widespread implementation of such an internally and externally validated model patients at high risk for infection after instrumented spine surgery can be discussed to minimize the risk of SSIs. For example, these patients can be advised conservative treatment or less invasive treatment without instrumentation. In cases that instrumented surgery is still indicated, patients could be better optimized before operation: e.g., lower body mass index, optimize diabetic regulation, stop using NSAID's, stop smoking, optimize nutritional depletion and improve physical performance in order to decrease the risk for SSI after surgery.(40)
In patients with or without optimized comorbidities who need instrumented spine surgery, alternative prophylactic antibiotic regimens can be considered to decrease the incidence of surgical site infections. Although there is still insufficient evidence for or against the specific alternative regimens that are efficacious, promising alternative regimens have been studied including intra-operative redosing of antibiotic prophylaxis, gram-negative coverage and the addition of intrawound application of vancomycin or gentamicin.(40)
Sweet et al. performed a retrospective comparative study to evaluate the safety and efficacy of adjunctive local application of vancomycin for infection prophylaxis in posterior instrumented thoracic and lumbar spine wounds as compared to intra-venous cephalexin alone. The reduction in wound infections was statistically significant ($p< 0.0001$). There were no adverse clinical outcomes or wound complications related to the local application of vancomycin. The authors concluded that adjunctive local application of vancomycin powder, used as an alternative to traditional antibiotic prophylaxis, decreases the postsurgical wound infection rate with statistical significance in posterior instrumented thoracolumbar spine fusions.(41)
With these data and the use of big databases, it should be possible to make better prediction models for decision making for orthopaedic treatment of the individual patient, like the model we made for the risk of

infection after instrumented spine infections. At present, few prediction models have been developed, but most of these models are still inadequate to be used in daily practice for decision making by orthopaedic surgeons.(42) In medical oncology, prediction models are widely used to analyse the survival per individual patient for a specific cancer, most of the time expressed in percentages for a specific period.
Such specific information for consultation of the individual patient on success or risk of complications after a joint prosthesis or after a spine procedure is not yet available in orthopaedics. However, considering the large populations of these joint or spinal procedures, big data analysis, and with the recent introduction of digital health applications it should be possible to collect multiple data from patients a long time before, during and after these orthopaedic procedures. With these big data and with the use of artificial intelligence it should be feasible to develop better prediction models that make individualized diagnostic or prognostic risk predictions for standard orthopaedic interventions.(43)
These prediction models will allow us in the near future to individualize treatment and after-treatment with the goal to optimize success of surgery with the prevention of complications and dissatisfied outcome.

In the sixth aim of this thesis we identify the pharmacokinetic release profile of the several local antibiotics that we used in our orthopaedic infection protocols as described in the first chapters (antibiotic impregnated beads and spacers). We described the elution of antibiotics from PMMA beads and from several spacers during time analysed by an ELISA (enzyme-linked immunosorbent assays) detection methodology.
The release of gentamicin from spacers reached a maximum in the first 24 hours. After a gentamicin burst release in the first 24 hours, there is a plateau phase with a significantly lower prolonged release of gentamicin. This is comparable to the findings in other studies on gentamicin elution from spacers.(44–46)
Compared to the release of gentamicin, the exact release of vancomycin from spacers in the clinical samples is much lower. In contrast to the gentamicin release, the pharmacokinetic release profiles of vancomycin showed a gradual increase of vancomycin release, without a plateau phase, in the first 5 to 7 days. This is in accordance with the findings from Bertazzoni Minelli et al, who showed lower exact release values and a longer burst release of vancomycin compared to gentamicin.(44)
The release of gentamicin from beads is reaching a plateau phase after 10-14 days, which is much later than that of spacers. The exact release values of beads are also more than 10 times higher compared to the release of gentamicin of spacers. This is comparable to literature.(46)
In comparison to antibiotic loaded PMMA beads, spacers have a relatively low maximum antibiotic concentration and their antibiotic release time above MIC is shorter.(10,46)
Spacers are mainly useful to maintain a better joint function in long interval infection treatment, but compared to gentamicin beads, the last aim of this thesis confirms that spacers are less preferable to use for treatment of the infection itself compare to Gentamycin beads, since they result in lower local gentamicin exudate levels.
In long interval 2 stage joint infection treatment a disadvantage of gentamicin beads is that beads are less comfortable than spacers and cannot preserve the joint space and lengthening of the soft tissue as spacers can. Another disadvantage of gentamicin beads used as local antibiotics in 'in situ' treatment is that you need an extra operation to remove the beads. Unfortunately these 2 disadvantages makes the use of gentamicin beads in infection treatment of joint prosthesis less attractive in the last decade whereby the advantage of a high local antibiotic concentration is also lost.
For future use, resorbable beads would be the solution to avoid an extra operation for removing the beads and taking advantage of the high antibiotic release.(47,48)
For future research these resorbable beads should also be examined for pharmacokinetic release profiles and hopefully show the same high release values of antibiotics as the non resorbable beads we analyzed. To take

the advantage of the function of the spacer and the high antibiotic concentration of gentabeads it is also possible to combine both local antibiotics.(49)

Concluding remarks and future perspectives

Surgical site infection after an orthopaedic procedure with implants is a very devastating complication with serious consequences as revision surgery, long time antibiotic treatment, an increase of hospital stay and health care costs. Also, more important for the individual patient, it gives high rates of morbidity and mortality and a negative impact on clinical outcome.

Therefor it is important to reduce the incidence of infections as much as possible. Prediction models like we validated and developed in this thesis can be helpful to minimize the risk of infection after an orthopaedic procedure. Patients with high risk prediction for infection for a specific procedure can be advised to treat conservative or less invasive to prevent the devastating complications of the more invasive treatment. Also risk factors can be reduced first before operation.

With big data analyses and with the use of artificial intelligence it should be feasible to develop more prediction models in future to individualize treatment and after-treatment with the goal to optimize success of treatment, and prevent complications and dissatisfied outcome.

If infections occur after an orthopaedic implantation, we described a successful infection treatment for surgical site infections after hip and knee prosthesis and after instrumented spinal procedures. This treatment includes gentamycin beads as local antibiotics to maximize the antibiotic level at the site of the infection.

To confirm this high level of local antibiotics we studied the release of different local antibiotics (spacers and beads). With ELISA we showed that the release values of gentamycin impregnated beads are more than 10 times higher compare to the release of gentamicin of spacers.

Besides the high success rate of the infection treatment with additional use of local gentamycin beads, a disadvantage of the gentamycin beads is the need for an extra operation to remove them. In future research this disadvantage can be solved by the use of resorbable antibiotic impregnated beads. Also other antibiotics than gentamycin or the additional use of other technics like antibiofilm coatings and biofilm deconstructive wound lavage can be studied in future to maximize the success rate of infection treatment after orthopaedic implant infection.

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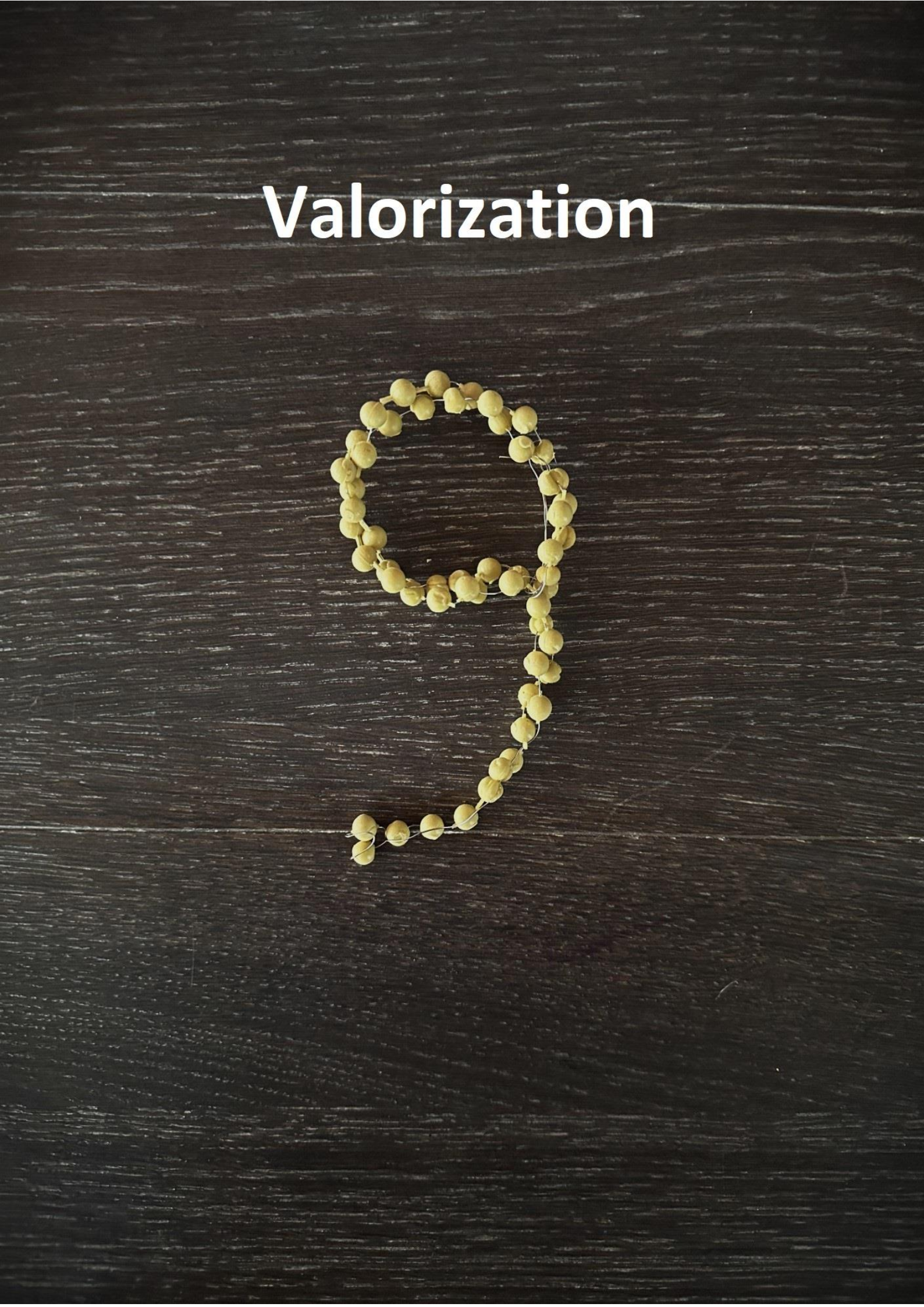
Valorization



Chapter IX

Valorization

Impact paragraph

Over the last 7 years, the LROI (national register for joint arthroplasty in the Netherlands) witnessed a growth of total hip joint replacements (THP) by 1000 cases/year (from 23,000 to 30,000) and by 1200 cases/year for total knee arthroplasty (TKP) procedures (from 20,500 to 29,000) (LROI 2018).
Also the number of patients undergoing spinal fusion has increased tremendously in the last decades with more invasive, complex procedures, in younger but foremost older patients and more revision procedures.(1–4)

Because orthopaedic procedures such as total joint replacements and instrumented spinal fusion have shown good results, limiting pain and improving functioning and quality of life, a further rise of performance of these procedures in the coming decades in Western society is expected, (LROI 2018).(2,3)

Unfortunately, the use of orthopaedic implants bears an inherent risk for bacterial infection. In literature the incidence of surgical site infection (SSI) after spinal surgery ranges from 2 to 12%, depending on diagnosis, surgical approach, the use of spinal instrumentation, and the complexity of the procedure.(5–7) The incidence of prosthetic joint infection ranges between 1-2% in literature and appears to be increasing just as the incidence of SSI after spinal surgery.(8)

Postoperative infections after instrumented orthopaedic surgery may have devastating consequences such as spinal non-union, osteomyelitis, implant loosening, sepsis, multi organ dysfunction and even death. Hospital stay may increase with 5.8 to 17 extra days and patients with orthopaedic surgical site infections (SSI) also utilize more healthcare resources, including outpatient and emergency department visits, radiology, and home health aides. Consequently, the financial burden is more than twice as high for cases with a SSI compared to patients without SSI.(9,10)
The costs of revision procedures caused by infection are expected to further increase in the near future and treatment is becoming more complex because of more complicated infections by the emergence of new resistant bacterial strains as well as infections with rare organisms.(11–13)

When compared with patients with uncomplicated joint arthroplasty, patients with infection scored significantly lower in satisfaction scales. (14) Also patients with SSI after spine surgery have substantially greater physical limitations and a distinct decrease in quality of life.(9,15)

In this thesis we described and analysed an infection treatment algorithm using gentamycin loaded beads for local antibiotic treatment for hip and knee prosthesis and for infections after instrumented spine surgery. The treatment protocols showed high success rates and the additional use of gentamicin impregnated beads, which lead to a very high local concentration of antibiotics could especially be useful in cases when instrumentation cannot be removed or in case of infection with highly resistant microorganisms. In this way, the use of local antibiotic delivery may help reduce the devastating economic and social consequences and associated outcomes of an SSI after surgery.
In future research, the use of resorbable antibiotic impregnated beads should be studied in order to avoid the extra operation of removal of the beads. Also the antibiotic release of other antibiotics than gentamicin and

vancomycin should be studied knowing that there is an increase of difficult to treat microorganisms with more antibiotic resistant patterns in orthopedic infections. The method of determining antibiotic release patterns of impregnated beads described in this thesis has been proven reliable and could well be used to analyze the release kinematics of other local antibiotics as well as in other material properties of the beads.
By the introduction of new technics and products like antibacterial or antibiofilm coatings and biofilm deconstructive wound lavage our infection treatment can be even more successful in future and decrease financial and clinical consequences of orthopedic infections.(16–18)

Apart from improving treatment for surgical site infections (SSIs) of orthopedic implants, an even better approach would be if we could prevent an SSI from happening. For this purpose, we externally validated an existing prediction model and developed and internally validated a new prediction model, specifically for our cohort of patients with instrumented spine surgery. The nomogram can already be downloaded for free: https://www.evidencio.com/validations/show/330
After an external validation of this prediction model, its performance can be improved and further implemented for widespread use in clinical practice in preoperative setting, where patients can fill in the model that results in a risk of infection. Together with the physician it is possible to identify patients at high risk of SSI and with shared decision making possibly prevent devastating consequences and associated outcomes of an SSI after surgery.
After implementation of such an internally and externally validated model, patients at high risk for infection after surgery can be discussed to prevent an infection.
By the analysis of 'big orthopaedic patient databases' using machine learning techniques, in future prediction models can be further improved to aid in decision making for orthopaedic treatment to an individual patient.

In contrast to infection populations there are already large populations of primary orthopaedic procedures useful for predictive models for outcome and complications.
At present, few prediction models have been developed, but most of these models are still inadequate to be used in daily practice for decision making by orthopaedic surgeons.(19)

In medical oncology and gynaecology, prediction models are widely used to analyse the survival per individual patient for a specific cancer or complications around childbirth.(20,21)

Such specific information for consultation of the individual patient on success or risk of complications after a joint prosthesis or after other orthopaedic procedures is not yet available in orthopaedics, despite the extensive data of these procedures. However, considering the large populations of these joint or spinal procedures, big data analysis, and with the recent introduction of digital health applications it should be possible to collect multiple data from patients a long time before, during and after these orthopaedic procedures. With these big data analyses and with the use of artificial intelligence it should be feasible to develop better prediction models that make individualized diagnostic or prognostic risk predictions for standard orthopaedic interventions.(22)
These prediction models will allow us in the near future to individualize treatment and after-treatment with the goal to optimize success of surgery, or other treatment, with the prevention of complications and dissatisfied outcome. By optimizing orthopaedic treatment also quality of life of individual patients will increase and costs can be reduced.

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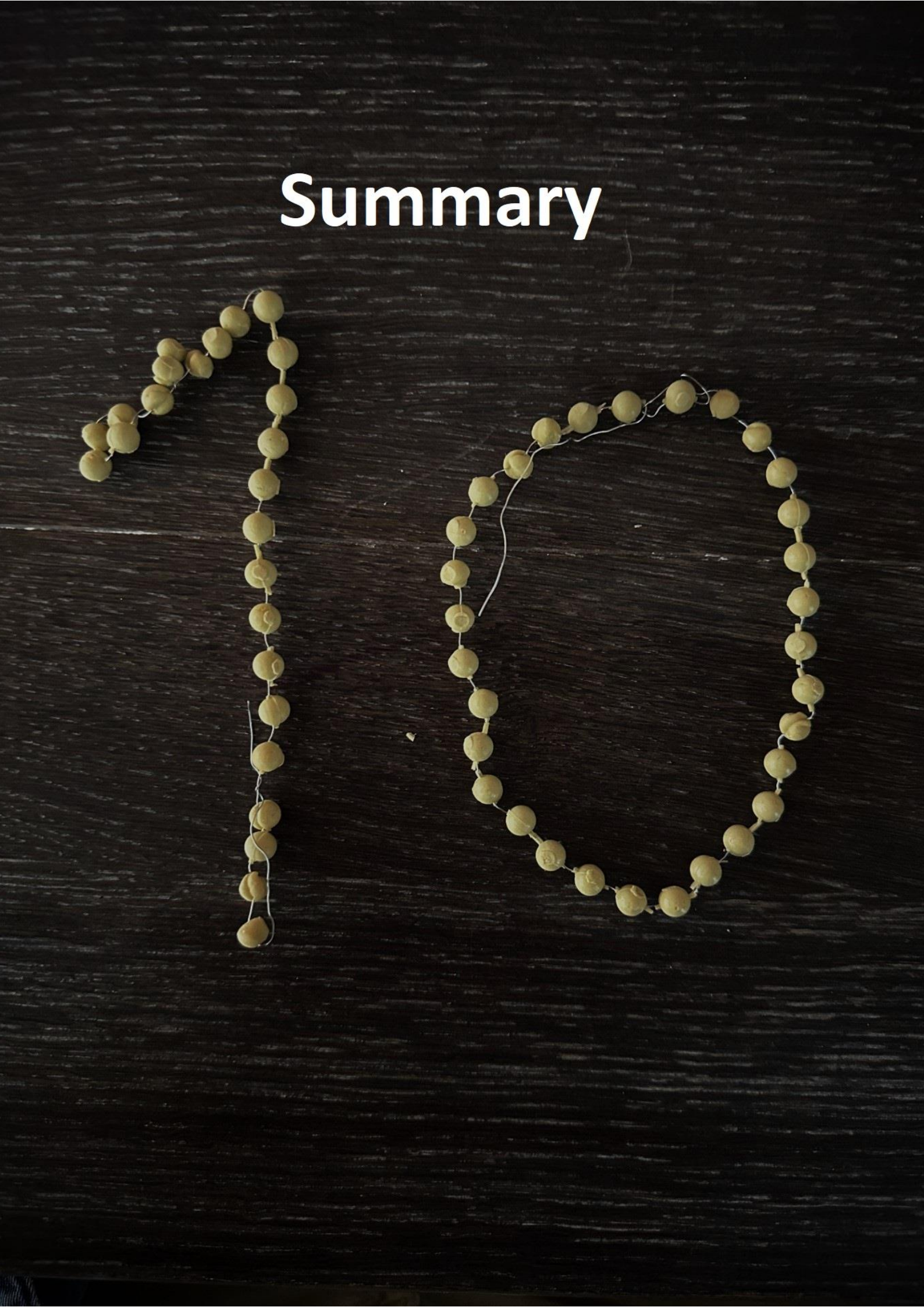
Summary



Chapter X

Summary
Because orthopaedic procedures with total joint prosthesis and instrumented spinal fusion have shown good results, with an increase of quality of life, a further increase of these procedures in the coming decades is expected, with more aged patients, more revision procedures, but also more younger patients who will undergo these procedures.

Unfortunately, orthopaedic implants have a risk for bacterial infection. In literature the incidence of surgical site infection (SSI) after spinal surgery ranges from 2 to 12%, depending on diagnosis, surgical approach, use of spinal instrumentation, and the complexity of the procedure. The incidence of prosthetic joint infection ranges between 1-2% in literature, and may be increasing just as the incidence of SSI after spinal surgery.

Even if the incidence rate of implant infections remains unchanged, the prevalence of implant infections will increase, with the increasing number and more complex orthopaedic implants procedures. It has been predicted that infection will become the most frequent mode of failure of total knee and hip arthroplasty.
Deep postoperative and hematogenous prosthesis infections may be treated with retention of the prosthesis, if the prosthesis is stable. How long the infection may be present to not exclude a good result is unclear.
In the second chapter we studied retrospectively 89 deep infected stable prostheses: 69 total hip and 20 total knee replacements; 83 early or delayed postoperative infections and 6 hematogenous. In postoperative infections, treatment started 12 days to 2 years after implantation, in hematogenous infections symptoms were present for 6-9 days. Patients were treated by debridement, prosthesis retention, systemic antibiotics and local antibiotics: gentamicin-PMMA beads or gentamicin-collagen fleeces. The minimum follow-up was 1.5 years. We analyzed how the result of the treatment was influenced by the length of the period the infection was present, and by other variables as host characteristics, infection stage and type of bacteria.
In postoperative infections the risk for failure increased with a longer postoperative interval: from 0.2 (CI 0.1-0.3) if the treatment started ≤4 weeks postoperative, to 0.5 (CI 0.2-0.8) if started ≤ 8 weeks. The relative risk for success was 0.6 (CI 0.3-1.0) if the treatment started ≤ 8 weeks. In the hematogenous group, 5 of 6 infections were treated successfully.

A longer delay before the start of the treatment causes an increased failure rate, but this must be weighed to the advantage of keeping the prosthesis. We consider a failure rate of < 50% as acceptable and therefore advocate to keep the prosthesis up to 8 weeks postoperatively, as well as in hematogenous infection with short duration of symptoms.

A 2-stage revision is the most common treatment for late deep prosthesis infections and in all cases of infected loosening. However there is no consensus about the optimal interval between the 2 stages.
In the third chapter we retrospectively studied 120 deep infected total hip (n=95) and knee (n=25) prostheses, treated during 24 years. The mean follow-up was 5 (2-20) years. All infections were treated with extraction, 1 or more debridements and with systemic and local antibiotics (gentamicin-PMMA beads). There were different intervals between extraction and reimplantation: median 14 (11-47) days in short term treatment with uninterrupted hospital stay, and 7 (3-22) months in long term treatment with temporary discharge. We analysed the outcome regarding infection healing and clinical results.
88% (105/120) of the infections healed, with no difference between short and long term treatment, 82 prostheses were reimplanted. In the last decade we treated patients more often with a long term treatment,

but reduced the discharge interval between the extraction and reimplantation. In long term treatments more reimplantations were performed compared with short term treatments, despite more difficult-to-treat infections with worse soft tissue condition.

Patient, wound and infection characteristics resulted in an individualized treatment with different intervals between stages. The 2-stage revision treatment in combination with local gentamicin PMMA beads resulted in good results in even difficult prosthesis infections and gentamicin resistant germs.
In contrast to knee and hip prosthesis infection there is no generally established treatment algorithm for the management of surgical site infection (SSI) and non-union after instrumented spinal surgery. In contrast to infected hip- and knee- arthroplasties, the use of a local gentamicin impregnated carrier in spinal surgery has not been widely reported in literature.

In the fourth chapter we described 48 deep SSI and non-union patients after instrumented spine surgery, treated between 1999 and 2016. The minimum follow-up was 1.5 years. All infections were treated with a treatment-regimen consisting of systemic antibiotics and repetitive surgical debridement, supplemented with local gentamicin releasing carriers.

We analysed the outcome of this treatment regimen with regard to healing of the infection, as well as patient- and surgery-characteristics of failed and successfully treated patients. 42 of the 48 (87.5%) patients showed successful resolution of the SSI without recurrence with a stable spine at the end of treatment. 36 patients' SSI were treated with debridement, local antibiotics, and retention or eventual restabilization of the instrumentation in case of loosening. 3 patients were treated without local antibiotics because of very mild infection signs during the revision operation. 3 patients were treated with debridement, local antibiotics and removal of instrumentation, of which one of these patients was restabilized in a second procedure. Infection persisted or recurred in 6 patients. These patients had a worse physical status with a higher ASA-score. *Staphylococcus aureus* was the most frequent causative microorganism.

We see that debridement and retention of the instrumentation, in combination with systemic antibiotics and the addition of local antibiotics provided a successful treatment for SSI and non-union after instrumented spinal fusion.

The rate of a surgical infection is relatively high after instrumented spine surgery. The availability of an easy-to-use prediction model would be of great help to select those patients that are at highest risk and probably prevent the devastating consequences of an infection.

After literature search in spine surgery, one prediction model was found that used only few predictors to estimate an individual's probability of a surgical site infection. Lee et al. developed a prediction model for SSI after spine surgery that was derived from a surgical spine register of the USA (The Spine End Result Registry).

In the fifth chapter we external validate this previously published prediction model for surgical site infection after spine surgery in our patient population, a Western European cohort of patients that underwent instrumented thoracolumbar spine surgery in a university hospital.

We included 898 consecutive patients who underwent instrumented thoracolumbar spine surgery. To quantify overall performance using Nagelkerke's R^2 statistic, the discriminative ability was quantified as the area under

the receiver operating characteristic curve (AUC). We computed the calibration slope of the calibration plot, to judge prediction accuracy.
Sixty patients developed an SSI. The overall performance of the prediction model in our population was poor: Nagelkerke's R^2 was 0.01. The AUC was 0.61 (95% confidence interval (CI): 0.54 – 0.68). The estimated slope of the calibration plot was 0.52.
Our conclusion was that the previously published prediction model showed poor performance in our academic external validation cohort. To predict SSI after instrumented thoracolumbar spine surgery for the present population, a better fitting prediction model should be developed.

In the sixth chapter we described the development including internal validation of a multivariable model for accurate prediction of surgical site infection (SSI) after instrumented spine surgery using a large cohort of a Western European academic center.

Data of potential predictor variables was collected in 898 adult patients who underwent instrumented posterior fusion of the thoracolumbar spine.
We used logistic regression analysis to develop the prediction model for SSI.
The ability to discriminate between those who developed SSI and those who did not was quantified as the area under the receiver operating characteristic curve (AUC). Model calibration was evaluated by visual inspection of the calibration plot, and by computing the Hosmer and Lemeshow goodness-of-fit test.

*S*ixty patients (6.7%) were diagnosed with an SSI. After backward stepwise elimination of predictor variables we formulated a model in which an individual's risk of an SSI can be computed. Age, body mass index, ASA score, degenerative or revision surgery and NSAID use appeared to be independent predictor variables for the risk of SSI.
The (AUC) was 0.72 (95% CI: 0.65 – 0.79), indicating reasonable discriminative ability.

The new developed prediction model for SSI after instrumented thoracolumbar spine surgery showed reasonable discriminative ability and calibration. Identification of patients at risk for SSI allows for individualized patient risk assessment with better patient-specific counseling, and may accelerate the implementation of multi-disciplinary strategies for reduction of SSI.

In the seventh chapter we determine *in vitro* and *in vivo* pharmacokinetic release profile of antibiotics from PMMA spacers and PMMA beads we used in aforementioned studies.
For the *in vitro* experiment the PMMA spacers or beads were submerged in phosphate-buffered saline and gentamicin concentrations were determined from collected specimen at several times points, measured with ELISA.

To assess the *in vivo* antibiotic release profile of different spacers, wound drainage fluid samples were collected after implantation of a spacer over a period of maximum 14 days.
After 48 hours the burst gentamicin concentration elution was 9,862 ± 1,782 ng/ml (mean ± SD) from spacers vs. 38,394 ± 7,071 ng/ml (mean ± SD) for beads. Over 35 days, spacers had eluted a cumulative mean concentration of 13,812 ± 3,548 ng/ml vs. 55,048 ± 12,006 ng/ml for beads (P<0.001).
Clinical samples of patients with a Vancogenx® spacer showed higher gentamicin release than Refobacin™ spacers (P<0.001).

Our study was the first that measured the release data of local antibiotics with ELISA. Compare to spacers, the exact release values of gentamicin from PMMA beads are more than 10 times higher and reached a maximum much later than spacers. This makes the use of PMMA beads more preferable to use for treatment of the infection itself.

Curriculum Vitae
Publications

Curriculum Vitae

Personalia

Daniël Janssen
28-02-1982/Eys

Opleidingen

2011-2017	Opleiding Orthopedisch chirurg (regio Zuid Nederland)
2004-2010	Geneeskunde, Universiteit Maastricht.
2000-2005	Fysiotherapie, Hogeschool Zuyd te Heerlen
1994-2000.1	VWO, Sophianum te Gulpen.

Diploma's

31/08/2010	Geneeskunde, Universiteit Maastricht. BIG: 89064308001
31/03/2005	Bachelor of Physiotherapy, Hogeschool Zuyd te Heerlen. BIG: 29064308004
28/06/2000	VWO, Sophianum te Gulpen

Medische werkervaring

01/01/2020 – heden	Staflid associatie Orthopedie, St Trudo ziekenhuis, St Truiden. België (Schouder/Knie/Enkel (sport))
01/09/2019 – 31/12/2019	Travelling fellowschip 'enkel sport/arthroscopie': AZ turnhout; AZ herentals, Chirec Delta Ziekenhuis/Foot and Ankle Institute, Brussel; AMC, Amsterdam, Fortius Clinic, Londen; Trofa Saúde Gaia, Porto
01/08/2018 – 31/08/2019	Fellowship orthopedie 'knie en schouder', St Trudo ziekenhuis, St Truiden. België
01/07/2017 – 30-06-2018	Fellowship orthopedie 'knie en schouder', AZ Monica, Antwerpen. België
01/01/2015 – 01/01/2018	Bestuur landelijke jongerenvereniging orthopedie Nederland, VOCA (Vereniging Orthopedisch Chirurgie Assistenten)

Opleiding Orthopedie

01/01/2013 – 30/06/2014	Arts Assistent in Opleiding (AIOS) "orthopedie", MUMC, Maastricht
01/07/2014 – 30/06/2015	Arts Assistent in Opleiding (AIOS) "orthopedie", Zuyderland, Heerlen
01/07/2015 – 30/06/2016	Arts Assistent in Opleiding (AIOS) "orthopedie", Zuyderland, Sittard
01/07/2016 – 30/06/2017	Arts Assistent in Opleiding (AIOS) "orthopedie", MUMC, Maastricht
01/01/2011 – 30/06/2011	Arts Assistent Niet in Opleiding (ANIOS) "algemene chirugie", Zuderland, Sittard (Dr. Tonn Hoofwijk)
15/09/2010 – 15/12/2010	Arts-onderzoeker CTCM te Maastricht Universitair Medisch Centrum, Maastricht. (Prof. Dr. Lodewijk van Rhijn)
2006 - 2009	Assistent bij orthopedische operaties in het Betlehem krankenhaus te Stolberg (Dr. Med. Andreas Bremer/Prof. Dr. Klaus Bläsius).
2004 - 2009	Fysiotherapeut in praktijk Diplan, Laurensberg, Aken (Drs. Stefan Rutten)

Overige Publicaties/Wetenschap

2013	Geen longvaattekening na thoraxtrauma. DMC. Janssen, T. Hoofwijk. Medisch contact. **Published**
2013	A women with a painful groin, Hernia garengeot. DMC. Janssen, T. Hoofwijk. Nederlands Tijdschrift voor Geneeskunde. **Published**
2014	A comparison of hallux valgus angles assessed with computerised plantar pressure measurements, clinical examination and radiography in patients with diabetes. DMC. Janssen, AP. Sanders, NA. Guldemond, J. Hermus, GHIM. Walenkamp, LW. van Rhijn. Foot and Ankle Research. **Published**
2016	Congenital absence of the ACL DMC. Janssen, EJP. Jansen. Nederlands Tijdschrift voor Geneeskunde. **Published**
2020	Preliminary experience with an image-free handheld robot for total knee arthroplasty: 77 cases compared with a matched control group. P. Bollars, A. Boeckxstaens, J. Mievis, S. Kalaai, MGM. Schotanus, DMC. Janssen. European Journal Orthopaedic Surgery and Traumatology. **Published**
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