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The infected knee arthroplasty

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Thesis

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Contents

List of papers

The thesis is based on the following papers:

I. Stefánsdóttir A, Knutson K, Lidgren L, and Robertsson O. The time and type of deep infection after primary knee arthroplasty. Submitted.

II. Stefánsdóttir A, Johansson D, Knutson K, Lidgren L, and Robertsson O. Microbiology of the infected knee arthroplasty: Report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases. *Scandinavian Journal of Infectious Diseases* 2009; 41(11-12): 831-40.

III. Stefánsdóttir A, Knutson K, Lidgren L, and Robertsson O. 478 primary knee arthroplasties revised due to infection – a nationwide report. Submitted.

IV. Stefánsdóttir A, Robertsson O, W-Dahl A, Kiernan S, Gustafson P, and Lidgren L. Inadequate timing of prophylactic antibiotics in orthopedic surgery. We can do better. *Acta Orthopaedica* 2009; 80(6): 633-8.

Definitions and abbreviations

Biofilm Organised communities of aggregated bacteria embedded in a hydrated matrix of extracellular polymeric substances

CNS Coagulase-negative staphylococci

cfu Colony-forming unit. A measure of the number of viable bacteria. In air expressed as cfu/m^3

CRR Cumulative revision rate

Index operation First-time revision, due to an infection

MIC Minimum inhibitory concentration: the lowest concentration of an antimicrobial substance that will inhibit the visible growth of a microorganism after overnight incubation

MRSA Methicillin-resistant *Staphylococcus aureus*

OA Osteoarthritis

PCR Polymerase chain reaction: a technique for in vitro amplification of specific DNA sequences from organisms, including bacteria.

PMMA Poly(methyl methacrylate): bone cement

Primary arthroplasty The first time one or more joint surfaces are resurfaced with prosthetic implant(s)

RA Rheumatoid arthritis

Revision arthroplasty A reoperation during which prosthetic component(s) are either exchanged, removed, or added

RR Risk ratio

SKAR The Swedish Knee Arthroplasty Register

SSI Surgical site infection

TKA Tricompartmental knee arthroplasty

UKA Unicompartmental knee arthroplasty

Introduction

Historical background

The development of modern knee arthroplasty started in the 1940s. In 1953 Walldius, an orthopaedic surgeon in Stockholm, described promising results with the use of a hinge prosthesis made of acrylate (Walldius 1953). Even though aseptic and antiseptic techniques were well implemented at this time, infection was a significant problem. In his series of 32 arthroplasties, performed on 26 patients, Walldius reported fatal septicaemia in 1 case, amputation due to infection in 2 cases, and arthrodesis due to infection in 4 cases (Walldius 1957). Sir John Charnley, the great pioneer in hip arthroplasty, addressed the infection problem by developing an operating theatre with ultra-clean air and a body exhaust system. By these measures, the infection rate after hip arthroplasty was brought down from more than 7% to 0.6% (Charnley 1979). In the early 1970s the principles of low-friction arthroplasty were applied to the knee joint (Insall et al. 1976), and with continuing development knee arthroplasty has become a routine operation that is performed on a large scale throughout the industrialised world.

The Swedish Knee Arthroplasty Register

The Swedish Knee Arthroplasty Register (SKAR) was established in 1975 by the Swedish Orthopaedic Society, and it was the first national arthroplasty register. The main aims were to give early warning of inferior designs and to present average results based on the experience of a whole nation instead of that of highly specialised units (Robertsson et al. 2000b). Currently there are 76 orthopaedics departments in Sweden that perform knee arthroplasties, and all report to the register. In September 2010, the database contained information on 165,000 primary knee arthroplasties and 12,450 revision knee arthroplasties. The main outcome variable reported by the register is revision arthroplasty, which is defined as any later operation after a primary knee arthroplasty that involves addition, exchange, or removal of at least one prosthetic component (including arthrodesis and amputation). The reason for revision is recorded based on a report from the operating surgeon and information retrieved from hospital records. In a validity study, it was estimated that 94% of revisions were accounted for (Robertsson et al. 1999).

Definition of infected knee arthroplasty

No standardised criteria of infected knee arthroplasty are available. The finding of a microorganism in cultures from tissue biopsies has been referred to as the gold standard (Banit et al. 2002), but some authors have instead used histological criteria of infection (Atkins et al. 1998). It is well known that in some cases of infected knee arthroplasty, culture fails to reveal any microorganism – and the possibility of false-positive cultures must also be considered. 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 prosthetic implant. An anatomy-based nomenclature scheme of nosocomial surgical site infections (SSIs) was presented by the Centers for Disease Control (CDC) in 1992 (Horan et al. 1992), and this is now widely used for surveillance (Morgan et al. 2005, Barnes et al. 2006). According to this scheme, SSIs are divided into incisional SSIs and organ/space SSIs. Incisional SSIs are further classified as involving only the skin and subcutaneous tissue (superficial incisional SSIs) or involving deep soft tissues (i.e. fascial and muscle layers) of the incision (deep incisional SSIs). To be classified as an organ/space SSI, the infection has to occur within 1 year of implantation and it should appear to be related to the procedure (Horan et al. 1992). In the case of infected

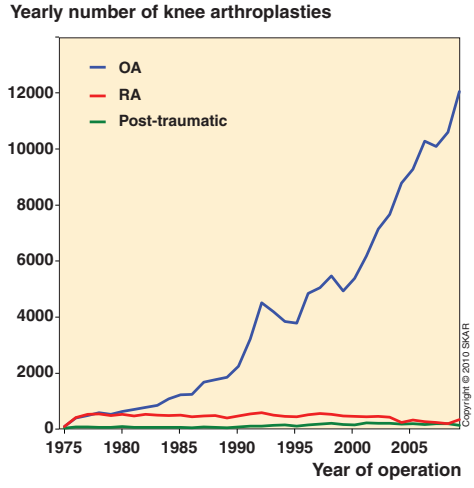

Figure 1. The annual number of arthroplasties for different diagnoses registered in the SKAR. From the SKAR Annual report 2010, available at www.knee.se.

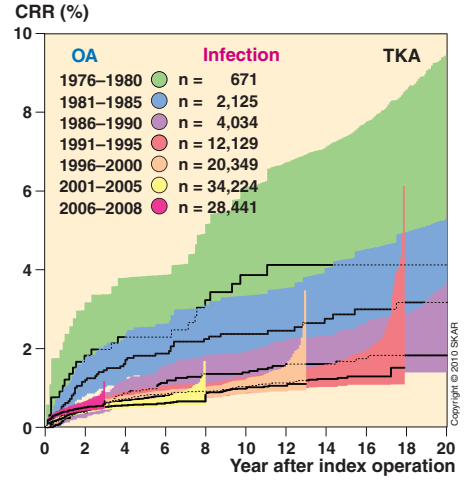

Figure 2. The CRR because of infection in OA patients undergoing primary TKA during different time periods. From the SKAR Annual report 2010, available at www.knee.se.

knee arthroplasty this nomenclature is confusing, as the largest part of the incision does not involve any muscle layer. In practice, there will be two classes: (1) superficial incisional SSI (involving skin and subcutaneous tissue), and (2) organ/space SSI (involving the joint, with the joint capsule as a natural boundary). In this work the organ/space SSI is termed infected knee arthroplasty.

The size of the problem

Despite the large number of operations performed each year, it is difficult to obtain reliable information on the incidence of infected knee arthroplasty. The national arthroplasty registers provide some information, but it must be remembered that there can be methodological differences between registers. Of the 34,701 primary knee arthroplasties (both total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA)) reported to the SKAR during 1999–2003, 0.65% were revised due to infection within 5 years. 29,928 were primary TKAs and 0.70% of them were revised because of infection within 5 years (personal information from the SKAR, September 2010). Of 6,133 cemented TKAs reported to the Norwegian arthroplasty register during 1994–2000, 0.44% were revised because of infection within 5 years (Furnes et al. 2002). In Finland data from the Finnish Hospital Infection Program, the Finnish Arthroplasty Register, and the Finnish Patient Insurance Center were cross-matched and the infection rate for 5,921 cases of TKA performed during 1999–2004 was estimated to be 1.3% (Huotari et al. 2010). In the USA, the risk of infection after TKA was reported to be 1.55% within 2 years in 69,663 patients in the Medicare population, the infections being identified by ICD-9 codes (Kurtz et al. 2010). In that study, patients undergoing TKA because of a bone cancer, a fracture, or joint infection were excluded, as were patients younger than 65 years.

With the increasing number of primary knee arthroplasties (Figure 1), the number of infected cases will increase. It has been predicted that infection will become the most frequent mode of failure of total knee arthroplasty, with great economic consequences (Kurtz et al. 2007). In Denmark in 2008, infection was reported to be the most common reason for revision (32.1%) (DKR 2009), and in Australia in 17.1% of cases (AOANJRR 2009). In Sweden and in England, in 2009, infection was reported to be the cause of revision in 23% of cases (NJR 2010, SKAR 2010).

Data from the SKAR has been used to calculate the cumulative revision rate (CRR) due to infection in OA patients undergoing TKA (Figure 2). The

CRR due to infection decreased during the first time periods studied, but there was a slight increase in CRR in patients operated during the years 2006–2008, compared to those operated during the years 2001–2005.

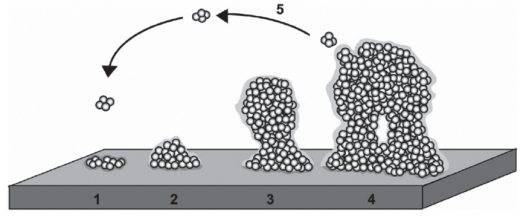

Figure 3. The development of a biofilm, depicted as a five-stage process. Stage 1: initial attachment of cells to the surface; stage 2: production of extracellular polymeric substances; stage 3: early development of biofilm architecture; stage 4: maturation of biofilm architecture; stage 5: dispersion of bacterial cells from the biofilm. From: Lasa I. International Microbiology 2006; 9: 21–28. Published with permission.

Classification

There is no consensus on a classification system for infected arthroplasties.

Zimmerli and co-workers have suggested that prosthetic joint infections should be classified as three types: early, delayed, and late infections depending on the time of appearance of the first signs and symptoms of infection (Zimmerli and Ochsner 2003). According to this scheme, early infections present during the first 3 months after surgery, delayed infections present between 3 months and 2 years, and late infections present 2 years or more after the arthroplasty. The late infections may appear either with a sudden systemic inflammatory response syndrome or without initial signs of sepsis, with a delayed course after a clinically unrecognised bacteraemia. This classification scheme highlights the pathogenesis and the presumed fact that most infections diagnosed within 2 years after primary arthroplasty are acquired during the perioperative period.

A classification system meant to be of assistance when selecting treatment was presented by Segawa and co-workers (Segawa et al. 1999), who defined an early postoperative infection as a wound infection (superficial or deep) that develops less than four weeks after the index operation. They defined a late chronic infection as one that develops four weeks or more after the index operation and has an insidious clinical presentation. They defined an acute haematogenous infection as one that is associated with a documented or suspected antecedent bactaeremia and that is characterised by acute onset of symptoms. In addition, they defined a separate group of infections: those that are clinically inapparent but where there are at least 2 positive cultures from specimens obtained at the time of a presumed aseptic revision (Segawa et al. 1999). An attempt at debridement with salvage of the prosthesis was recommended in early postoperative infections, and removal of the prosthesis in late (chronic) infections. This classification has been used in a staging system that has been shown to be predictive of outcome when treating infected knee arthroplasties (McPherson et al. 1999, Cierny and DiPasquale 2002).

Pathogenesis

How do bacteria aggregate in a biofilm and how do they live in it? The answers to these questions are central to our understanding of the pathogenesis of infected knee arthroplasty. A biofilm is defined as an organised community of aggregated bacteria embedded in a hydrated matrix of extracellular polymeric substances (Hall-Stoodley and Stoodley 2009). Biofilms can be formed by most, if not all, microorganisms and today the biofilm mode of life is regarded as the rule rather than the exception (Jefferson 2004, Lewis 2007, Coenye and Nelis 2010).

Biofilm formation is a multi-stage process (von Eiff et al. 2002) that starts with attachment of bacteria to the implant surface. At the same time, the implant is coated with proteins from the host, with which the bacteria can attach by specific surface proteins. The next step is proliferation and accumulation in multi-layered cell clusters, which are embedded in extracellular polymeric substances (containing polysaccharides, proteins, and DNA). As the biofilm matures, focal areas may dissolve and the liberated bacterial cells can spread to another location where new biofilms can be formed (Lasa 2006, Hoiby et al. 2010) (Figure 3). Bacte-

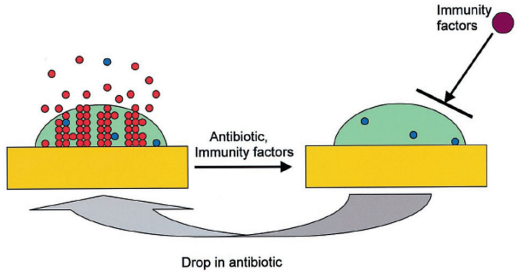

Figure 4. Model of biofilm resistance. An initial treatment with antibiotic kills planktonic bacterial cells and the majority of bacterial cells in the biofilm. The immune system kills planktonic persisters but the biofilm persister cells are protected from the host defenses by the exoplysaccharide matrix. After the antibiotic concentration drops, persisters resurrect the biofilm and the infection relapses. From: Lewis. Antimicrobial Agents and Chemotherapy 2001; 45(4): 999–1007. Published with permission.

rial cells embedded in the biofilm communicate with each other and show a coordinated group behaviour mediated by a process called quorum sensing (Coenye and Nelis 2010).

The extracellular polymeric substances protect the bacteria from the host's immune cells and restrict the diffusion of antimicrobials into the biofilm. Bacteria in the deeper layers of a thick biofilm have less access to nutrients and will grow more slowly, which reduces the effect of antibiotics active against proliferating bacteria. A subpopulation of the bacteria in the biofilm is named persisters, which are bacteria that are highly tolerant to antibiotics – even those active against slowly growing bacteria – and when the antibiotic concentration drops, the persisters resurrect the biofilm and there is relapse of infection (Figure 4) (Lewis 2001, Lewis 2007).

To start biofilm formation, bacteria must have access to the joint and there are several possible routes of entry. Bacteria, either from the patient's skin or from the surroundings, can contaminate the joint at the time of surgery. Bacteria can also gain access to the joint from an adjacent infection, either a postoperative superficial SSI or a later abscess around the knee joint. They can spread haematogenously from a distant focus, and finally, they can spread as an iatrogenic infection in conjunction with arthrocentesis, arthroscopy, or surgical intervention in the joint. The effect that the introduction of ultra-clean air and prophylactic antibiotics has had on the rate of infection emphasises the importance of intra-operative contamination (Lidwell et al. 1987).

Infecting microorganisms

Bacteria are responsible for the vast majority of knee arthroplasty infections, with occasional infections caused by fungi – most commonly a member of the genus Candida (Hennessy 1996). The bacteria most commonly found in infected knee arthroplasties are *Staphylococcus aureus (S. aureus)* and coagulase-negative staphylococci (CNS), of which *Staphylococcus epidermidis* in this context is the most important species.

It has been stated that early infections are caused by virulent microorganisms such as *S. aureus* and Gram-negative bacteria, whereas delayed (low-grade) infections are caused by less virulent microorganisms such as CNS and *Propionibacterium acnes* (Kamme et al. 1974, Zimmerli et al. 2004).

Risk factors

Men have a higher risk of revision because of infection than women (Figure 5a) (Robertsson et al. 2001, Furnes et al. 2002, Jämsen et al. 2009a), but the reason for this is unknown.

Rheumatoid patients have a higher risk of revision because of infection than OA patients (Figure 5b) (Robertsson et al. 2001, Schrama et al. 2010). The reason for this may be related to the disease and to the anti-rheumatic treatment. Glucocorticoid agents are known to increase the risk of infection (Bernatsky et al. 2007) whereas the effect of the new biological anti-rheumatic drugs on the incidence of infection following orthopaedic surgery has not been clarified (Giles et al. 2006, den Broeder et al. 2007).

Primary UKAs have a lower risk of revision because of infection than TKA (Figure 5c).

Obesity is a growing problem in many parts of the world, and at least in the USA the mean BMI of patients undergoing knee arthroplasty is rising (Fehring et al. 2007). In a study in which more than half of the patients had a BMI of ≥ 30 kg/m^2, obesity was a risk factor for infection (Namba

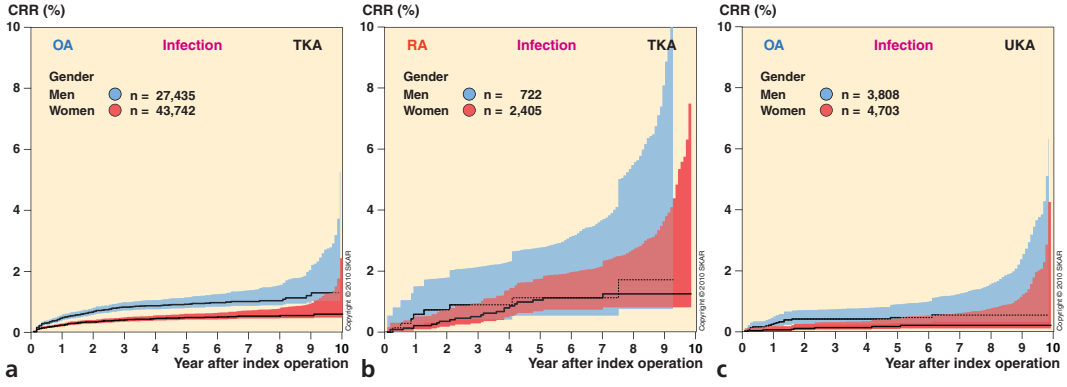

Figure 5. Using the endpoint "revision for infection", the CRR (1999–2008) shows in TKA for OA that men are more affected than women (RR = 2.0). The same tendency is true for RA, although not statistically significant. UKA with its smaller implant size does better than the larger TKA, but even in UKA men have 2.9 times the risk of women of becoming revised for infection. In TKA, patients with RA are more affected than those with OA (RR = 1.7). From the SKAR Annual report 2010, available at www.knee.se.

et al. 2005). Obese patients often have other comorbidities such as diabetes, which increases the risk of infection (Dowsey and Choong 2009). Preoperative hyperglycaemia has recently been shown to be predictive of infection after a primary knee arthroplasty (Jämsen et al. 2010).

Smoking may increase the risk of SSI (Mangram et al. 1999). In an interventional study, wound-related complications were found to be less frequent in the group of patients who had smoking intervention 6–8 weeks before scheduled hip or knee arthroplasty (Møller et al. 2002).

The risk of infection is increased in revision surgery, when constrained or hinged prostheses are used, and when there is a history of earlier fracture in the joint (Jämsen et al. 2009a).

Post-operative wound complications are a strong predictor of later diagnosis of infected arthroplasty (Wymenga et al. 1992b, Berbari et al. 1998, Jämsen et al. 2009a). It appears likely that many of these presumed superficial SSIs and wound complications were actually deep infections.

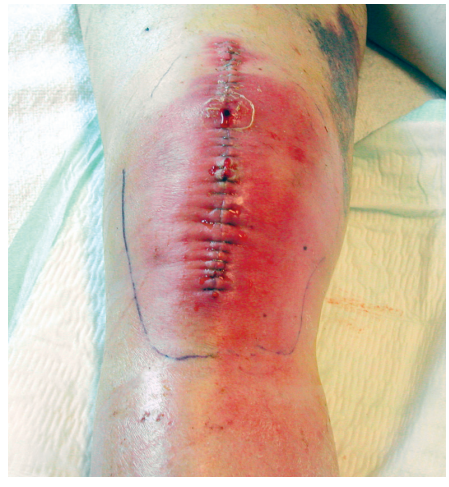

Figure 6. A 59-year-old man with OA attended hospital with fever (38°C) and a painful knee 14 days after undergoing primary knee arthroplasty. Open debridement was performed, and methicillin sensitive *S. aureus* was cultured from 5 out of 5 tissue biopsies. Antibiotic treatment started with i.v. cloxacillin, followed by p.o. ciprofloxacin and rifampicin. The infection could be eradicated and the implant retained. Published with permission from Bertil Christenson.

Diagnosis

There is a large variation in the symptoms and signs of infected knee arthroplasty, depending on the type of infection, the infecting microorganism, and the immunological status of the patient (Figures 6 and 7). The presence of – or a history of – post-operative wound complication should raise the degree of suspicion. In delayed and late infections, pain and/or stiffness may be the predominant complaint, often in conjunction with mild to moderate effusion in the joint.

The laboratory tests found to be of value are C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Sanzén and Carlsson 1989, Parvizi et al. 2008a). There is a normal rise in CRP

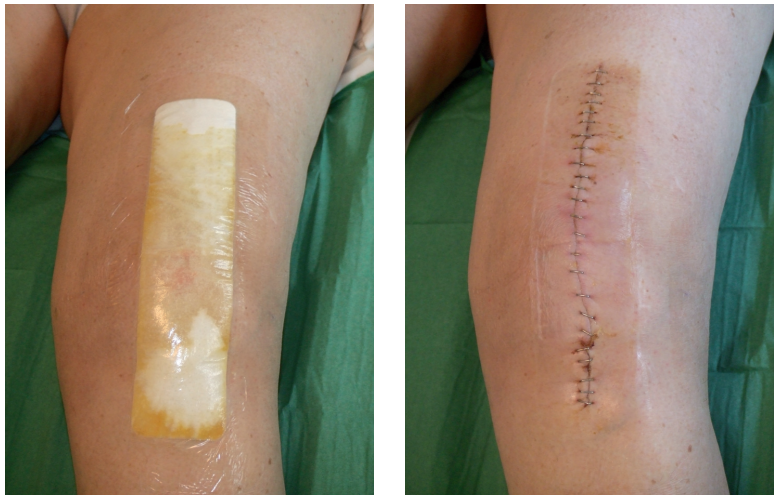

Figure 7. A 66-year-old woman with RA was treated with glucocorticoid, methotrexate, and remicade, and on the third day after undergoing primary knee arthroplasty she received p.o. flucloxacillin due to discharge from the wound. She attended hospital at day 16 (picture) because of continued discharge. Open debridement was performed, and methicillin resistant CNS was cultured in 5 out of 5 tissue biopsies. Antibiotic treatment started with i.v. vancomycin, followed by p.o. clindamycin and rifampicin. The infection could be eradicated and the implant retained.

in conjunction with surgery, with a peak on the second day (White et al. 1998), and near normalisation at the end of the second week (Niskanen et al. 1996). The level of synovial fluid IL-1 and IL-6 has recently been shown to differentiate patients with periprosthetic infection from patients with aseptic diagnosis (Deirmengian et al. 2010).

Plain radiographs are necessary to visualise the state of the implant, and to look for signs of periprosthetic bone destruction and loosening. Radionuclide imaging has been found to be helpful when differentiating between delayed or late infection and aseptic loosening, the combined leukocyte/marrow imaging being the recommended procedure (Love et al. 2009). The role of CT and MRI has been limited due to metal artefacts, but with technological advances these techniques may become useful (Sofka et al. 2006).

Analysis of synovial fluid is an essential part of investigation, and leukocyte differential of >65% neutrophils (or a leukocyte count of $>1.7 \times 10^9$/L) has been found to be a sensitive and specific test for the diagnosis of prosthetic knee infection in patients without underlying inflammatory joint disease (Trampuz et al. 2004). In another study, the cut-off values for optimal accuracy in diagnosis of prosthetic joint infection were found to be 1.1×10^9/L for fluid leukocyte count and 64% for neutrophil differential; when combined with CRP and ESR, infection could safely be excluded or confirmed (Parvizi et al. 2008a).

The sensitivity of synovial fluid culture has varied between 50% and 100% in different studies (Meermans and Haddad 2010). Blood culture bottles are recommended (Font-Vizcarra et al. 2010), and in the case of small amounts of fluid gained, a paediatric bottle can be used (Hughes et al. 2001).

In 1981, Kamme and Lindberg reported their experience with culture of biopsy samples, collected during revision hip arthroplasty, and recommended that five separate biopsy samples be taken (Kamme and Lindberg 1981). Other authors have come to the same conclusion (Atkins et al. 1998).

With the polymerase chain reaction (PCR) technique, bacteria can be identified by amplification of bacterial DNA containing the 16S rRNA gene. Despite interesting reports during the 1990s (Mariani et al. 1996, Tunney et al. 1999), the technique still has a limited role in diagnosing infected knee arthroplasty (De Man et al. 2009, Del Pozo and Patel 2009) .

Intraoperative gram staining has repeatedly been shown to lack sensitivity and is not recommended (Morgan et al. 2009).

Histology has been considered to be the most reliable method in diagnosing arthroplasty infection (Atkins et al. 1998), but it is not standardised and the inter-observer variability is high (Zimmerli et al. 2004).

The American Academy of Orthopaedic Surgeons has recently published extensive guidelines for the diagnosis of periprosthetic joint infections of the hip and knee (AAOS 2010).

Treatment

Successful treatment of infected knee arthroplasty involves eradication of the infection along with preservation of function in a pain-free knee joint. This may be achieved by early debridement with retention of the implant or revision arthroplasty in one or two stages. In certain circumstances, the treatment is limited to limb saving, with an arthrodesis or extraction of the implant as options, and under exceptional circumstances the only alternative is above-the-knee amputation. There are cases in which suppressive antibiotic treatment is used to maintain function in a chronically infected joint.

Algorithms have been developed to be of help when choosing treatment (Zimmerli et al. 2004), and favourable outcome has been coupled to adherence to the algorithm (Laffer et al. 2006).

Debridement involves arthrotomy, removal of all debris and inflamed synovial membranes, if possible exchange of the tibial insert (which makes access to the posterior part of the joint possible) and lavage with a large amount of fluid. The probability of eradicating the infection is related to the time the biofilm has had to establish itself and mature. It is still not clear what cases it would be reasonable to try to treat with debridement. A duration of less than 4 weeks has been recommended as a time limit (Schoifet and Morrey 1990, Segawa et al. 1999), whereas in other studies the limit has been set at 2 weeks (Borden and Gearen 1987, Teeny et al. 1990, Burger et al. 1991, Wasielewski et al. 1996). It has even been reported that debridement more than 2 days after the onset of symptoms may be associated with a higher probability of treatment failure compared to debridement within 2 days of onset (Brandt et al. 1997). Better results have been reported when rifampcicin (which inhibits bacterial RNA polymerase) has been included in the antibiotic treatment used in conjunction with debridment of a stable implant (Zimmerli et al. 1998, Berdal et al. 2005, Soriano et al. 2006, Aboltins et al. 2007), but it is still not clear for how long after surgery this strategy can be used. In the study by Zimmerli and co-workers, the longest duration of symptoms was 21 days whereas in the other studies the protocol allowed inclusion of infections diagnosed within 3 months.

Revision arthroplasty can be performed in one or two stages. In a review paper published in 2009, Jämsen and co-workers summarised the results of one- and two-stage revision arthroplasties and found that the overall success rate in eradication of infection was 73–100% after one-stage revision and 82–100% after two-stage revision (Jämsen et al. 2009b). Comparison of the two methods is, however, difficult due to differences in selection.

Two-stage revision arthroplasty may also be performed in different ways. Initially, the joint was left empty during the interval between stage one and stage two (Insall et al. 1983). Beads made of antibiotic-loaded bone cement were then introduced, which allowed local administration of antibiotics in the joint (Borden and Gearen 1987). With the use of a spacer block, made of antibiotic-loaded bone cement, it was possible to preserve the length of the leg, prevent adhesion of the patella to the femur, and thereby make stage two easier to perform (Cohen et al. 1988). An articulating spacer (Figure 8), with separate tibial and femoral components, probably gives better patient comfort and the range of motion after stage two may become better (Hofmann et al. 1995, Fehring et al. 2000, Jämsen et al. 2009b).

Arthrodesis can be performed in one or two stages. During the time of healing, it can be fixated using either external or internal fixation, an intramedullary rod being the most common type of internal fixation (Knutson et al. 1984, Conway et al. 2004). Better results, with respect to eradication of infection, have been reported with the use of external fixation (Figure 9) whereas the rate of healing of the arthrodesis is higher with the use of an intramedullary rod (Mabry et al. 2007).

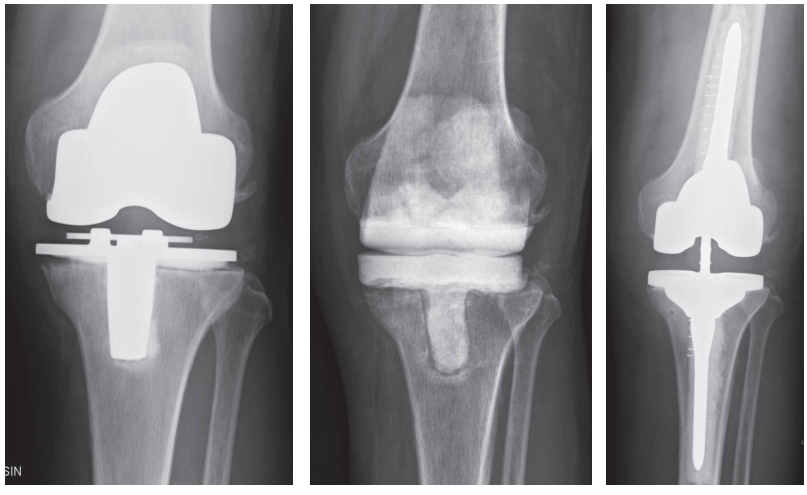

Figure 8. A 77-year-old man with OA who had an early infection with methicillin-resistant CNS after a primary knee arthroplasty. Open debridement failed, and radiographs at 7 weeks after primary surgery revealed periprosthetic bone destruction (see above). He went through a two-stage revision with the use of an articulating spacer made of vancomycin- and gentamicin-loaded bone cement. During the interval between stage 1 and 2, the antibiotic treatment consisted of i.v. vancomycin, followed by p.o. linezolid. The infection was eradicated.

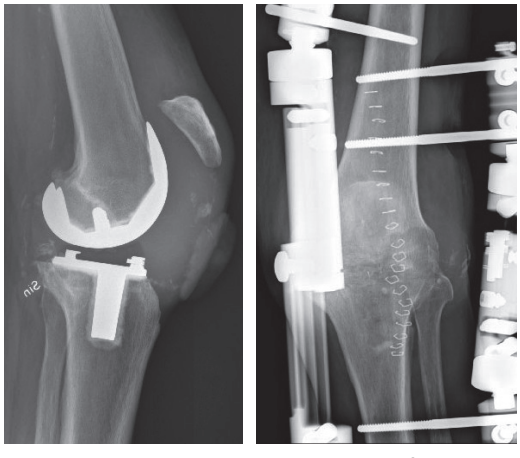

Figure 9. An 86 year-old-man with RA who fell and sustained a rupture of the patellar ligament twelve days after a primary knee arthroplasty. The joint became infected with 3 kinds of bacteria (*S. aureus, Proteus vulgaris*, and a *Haemophilus* species). Due to lack of a functioning extensor mechanism, arthrodesis was chosen as treatment with double Orthofix instruments used for external fixation. The patient died of cerebrovascular disease, before healing of the arthrodesis.

Extraction, or excision arthroplasty, can be considered in exceptional cases but it leaves the joint unstable and it is not certain that infection can be eradicated by extraction of the prosthesis.

Above-the-knee amputation may be the only alternative in the case of life-threatening sepsis or uncontrollable infection. Vascular disease in conjunction with infection may also lead to amputation. High mortality and poor functional result have been reported (Fedorka et al. 2010).

Suppressive antibiotic is an alternative for patients with chronic infection caused by a microorganism that can be suppressed with oral antibiotic(s), which can be given for long time without severe adverse effects (Segreti et al. 1998).

Effects on quality of life

Surprisingly little information is available on the effect that infected knee arthroplasty has on quality of life. When compared with patients with uncomplicated total joint arthroplasty, patients with infection scored significantly lower in satisfaction (visual analogue scale), WOMAC, AQoL, and all aspects of SF-36 other than general health and role limitations–emotional (Cahill et al. 2008). In a study in which 26 cases that were revised because of infection were compared with 92 cases that were revised for reasons other than infection, the objective results after septic revision were inferior to the

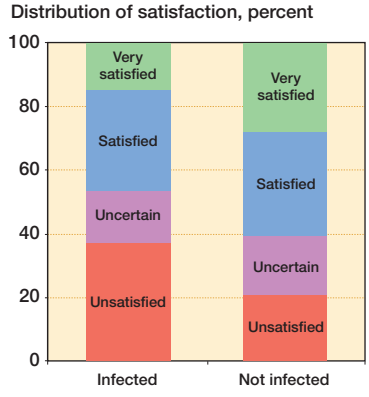

Figure 10. Results from a postal survey in 1997, answered by patients who had undergone primary knee arthroplasty in the period 1981–1995 (Robertsson et al. 2000a). Of the revised cases, 47% of 232 patients who had revision for infection and 61% of 1,865 patients who had revision for other reasons were satisfied or very satisfied.

results after aseptic revision in terms of Knee Society clinical score, function score, range of motion, and return to activities of daily living (Barrack et al. 2000). In a study from the SKAR, 47% of those revised because of infection were satisfied or very satisfied, compared to 61% of those revised for other reasons (Figure 10) (Robertsson et al. 2000a).

Economic impact

In the USA the costs of prosthetic joint infections during the years 1997–2004 have been analysed, based on information from the National Hospital Discharge Survey. The annual adjusted diagnostic-related group (DRG) cost for such infection increased from $195 million to $283 million during these years, whereas the mean DRG reimbursement per hospitalisation of $9,034 did not change (Hellmann et al. 2010).

In another study from the USA, based on the Nationwide Inpatient Sample (NIS) database, the average total charge for those having a primary knee arthroplasty without an infection was $35,320 whereas the average total charge for those with infection was $63,705 (Kurtz et al. 2008). In a single-centre study, also from the USA, the mean charge for infected revision TKA was $109,805 whereas the mean charges for aseptic revision TKA was $55,911 (Lavernia et al. 2006). These figures are in line with an earlier study from the US where surgical treatment of the infected total knee implant required 3–4 times the resources of the hospital and the surgeon compared to a primary TKA, and approximately twice the resources of a non-septic revision arthroplasty (Hebert et al. 1996).

Apart from the direct costs related to hospitalisation, there are considerable indirect costs related to home care, nursing facilities, and antibiotics.

Antibiotic prophylaxis

The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels that exceed – for the duration of the operation – the minimum inhibitory concentrations (MICs) for the organisms likely to be encountered during the operation (Bratzler and Houck 2004).

The first study published on prophylactic antibiotics in joint replacements came from Sweden (Ericson et al. 1973). The effect of cloxacillin as prophylactic antibiotic in hip surgery was compared with a placebo, and in the treatment group there were no infections in 83 patients after 6 months of follow-up whereas there were 12 infections in the placebo group (8 superficial and 4 deep infections) ($p < 0.001$). A larger study with a longer follow-up confirmed the results and showed a lower rate of infection in the treatment group, even after a follow-up of more than 2 years (Carlsson et al. 1977). The effect of the first-generation cephalosporin cefazolin was proven in a multicentre study performed in France during the period 1975–1978 (Hill et al. 1981).

In a comparison between beta-lactam penicillin and a first-generation cephalosporin as a prophylaxis in hip arthroplasty, there was no difference found between the groups (Pollard et al. 1979). In this study, flucloxacillin was given intravenously for 24 hours followed by oral medication for 14 days, whereas cephaloridine was given as 3 intravenous doses over the first 12 hours, and the authors concluded that the simplicity of the 3-g cephaloridine regime was an advantage. Beta-lactam penicillin and a first-generation cephalosporin were compared in another study using the same dosage scheme for both types of antibiotics (1 g × 3) (Van Meirhaeghe et al. 1989). There was

no significant difference in infection rate between the study groups, but the groups were heterogeneous and the study lacked power.

There is now a general consensus that the length of antibiotic prophylaxis should not exceed 24 hours, but how many doses should be given has not been clarified. In a multi-centre study in the Netherlands, a one-dose regime with the second-generation cephalosporin cefuroxime was compared to 3 separate doses in patients undergoing a total hip replacement, hemiarthroplasty of the hip, or total knee replacement (Wymenga et al. 1992a). In the one-dose group, the infection rate was 0.83% (11/1,324) and in the 3-dose group it was 0.45% (6/1,327), but the difference was not statistically significant ($p = 0.17$). The authors concluded that a 3-dose regimen of cefuroxime was to be recommended until further data became available.

In a study from the Norwegian Arthroplasty Register, it was shown that the risk of revision for any reason was higher when one dose of antibiotic (as compared to 4 doses) was given within 24 hours, whereas there was no significant difference in the risk of revision between administration of 3 and 4 doses within 24 hours. When the endpoint was revision due to infection, no statistically significant difference was found (Engesaeter et al. 2003).

The timing of the pre-operative antibiotic prophylaxis is important (van Kasteren et al. 2007), especially when a tourniquet is used (Tomita and Motokawa 2007).

The risk of haematogenous infection in conjunction with dental procedures has been debated, but it is now clearly understood that antibiotic prophylaxis is not needed for all patients with total joint replacement prior to dental procedure (Berbari et al. 2010, Zimmerli and Sendi 2010).

Bone cement

The Australian arthroplasty register reported a lower rate of revision due to infection when antibiotic cement was used (0.67%) than when plain cement was used (0.91%) (AOANJRR 2009). The effect of antibiotic-loaded cement has been studied more thoroughly in primary hip replacement, where there has been convincing evidence of a reduced number of infections from using antibiotic-loaded bone cement (Engesaeter et al. 2003, Parvizi et al. 2008b).

Other prophylactic measures

In the 1960s and early 1970s antibiotics were seen as an alternative to ultra-clean air as operation boxes were not widely available. By combining ultra-clean air and antibiotics the incidence of sepsis after surgery was much less than that when either was used alone (Lidwell et al. 1987). With the low infection rates of today, it is extremely difficult to prove (or disprove) the effect of a single specific change in prophylactic measures by measuring infection rate. In the operating theatre, cfu/m^3 is used as a measure of the quality of the air, and this value should be less than 10.

A shower with chlorhexidine solution has been shown to effectively decrease bacterial counts on the skin (Byrne et al. 1991), and in Sweden at least two preoperative chlorhexidine showers are routine before knee arthroplasty surgery. It has, however, not been proven that this routine reduces the number of infections. In a recent study, preoperative screening to identify nasal carriers of *S. aureus* and subsequent treatment with nasal mupirocin and chlorhexidine soap reduced the number of infections (Bode et al. 2010). Other studies have shown that in people who are nasal carriers of *S. aureus*, the use of mupirocin ointment results in a statistically significant reduction in *S. aureus* infections (van Rijen et al. 2008), but possible resistance to mupirocin has to be monitored (Caffrey et al. 2010).

Other prophylactic measures include optimisation of the patient's condition prior to operation, minimising the length of stay at the hospital prior to operation, and strict addiction to hygiene routines.

Aims of the study

The aims of the study were:

1. to determine the timing and type of deep infection after a primary knee arthroplasty, and to evaluate the most commonly used classification systems;

2. to determine the microbiology of surgically revised infected primary knee arthroplasty and the antibiotic susceptibility patterns of the pathogens isolated;

3. to determine what type of surgical treatment Swedish orthopedic surgeons have used for infected knee arthroplasty;

4. to evaluate the results of surgical treatment of infected knee arthroplasty, and identify possible factors that may be predictive of the outcome;

5. to study the timing of administration of the first dose of prophylactic antibiotics in orthopaedic surgery.

Patients and methods

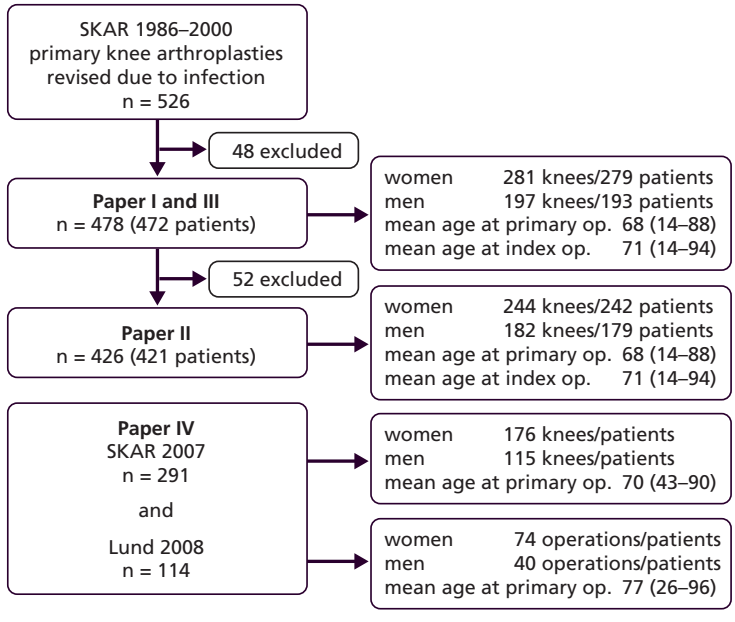

Figure 11. An overview of patient allocation.

Papers I–III

Patients who were included. Patients who had their primary knee arthroplasty revised for the first time during the years 1986–2000, due to deep infection, were included in the studies. No criteria had to be fulfilled other than that the treating surgeon had diagnosed the knee as being infected at the time of revision. This first revision was defined as the index operation. In December, 2003, the SKAR was searched for cases fulfilling this criterion and 526 cases were identified. During the study period, the national patient administrative system (PAS) was used to search for unreported revisions – minimising the risk of unreported revisions, in particular arthrodesis, extraction of the prosthesis, and amputation. Information on sex, age, primary diagnosis, primary operation, and revisions was gathered from the database of the registry. Information on co-morbidities, wound complications after the primary operation, type of infection, the infecting pathogen, its antimicrobial susceptibility pattern, surgical and antimicrobial treatment, and the results of treatment was gathered retrospectively from patient records, operation reports, and culture reports which were requested from the involved orthopaedics departments and microbiology laboratories involved.

Patients who were excluded. Of the 526 revisions, 48 knees (9.1%) were excluded. In 22 cases, the operating surgeon at the time of surgery suspected infection and, based on this report, the reason for revision was registered to be infection. A review of the medical records showed that infection could not be verified. Seven cases of debridement, which included exchange of the tibial polyethylene insert, were excluded since in the context of the study these operations were considered to be soft tissue operations and not true revisions. In 19 cases, aseptic revisions were wrongly recorded as infected revisions.

Patients. 478 first-time revisions of primary knee arthroplasties due to infection remained for study. An overview of patient allocation is given in Figure 11. Six patients had both knees revised because of infection and each knee was regarded

as a separate case. Osteoarthritis (OA) was the primary diagnosis in 299 patients (302 cases), rheumatoid arthritis (RA) was the primary diagnosis in 140 patients (143 cases), and other disease was the primary diagnosis in 33 patients (33 cases). Regarding gender, 54.6% of the OA cases and 67.8% of the RA cases were females. Today, OA is the predominant indication for knee arthroplasty; however, during the time of the study, patients with RA made up a larger proportion of those being operated (Figure 1). A modified Charnley's classification for the knee (Charnley 1979, Dunbar et al. 2004) was used as an estimate of co-morbidity and the patients were classified as group A (disease in the index knee only), group B (bilateral knee disease), or group C (remote arthritis and/or a medical condition that affected their ability to ambulate). 14% of the patients were noted to have diabetes.

The primary operations were performed at 75 orthopaedics departments, the first in 1976 (4 cases) and the most recent in 2000 (11 cases). There were 389 TKAs (81.4%), 65 UKAs (13.6%), 4 combined medial and lateral UKAs (0.8%), 17 hinged prostheses (3.6%), and 3 femuro-patellar prostheses (0.6%).

Bone cement was used for fixation in 96% of cases, but information about the type of cement used was available in only 45% of cases; of these, 90% contained antibiotic. Information on the type of systemic antibiotic prophylaxis used could not be extracted from the hospital records, but the most commonly used antibiotic prophylaxis in Sweden has been cloxacillin (SHPR 2009).

Information about wound complications was gathered from the hospital records, and it was available in 444 cases (92.9%). To be recorded as a wound complication, the wound disturbance had to have occurred during the first 30 days after primary operation and had to have been noted before deep infection was diagnosed. The wound complications were classified as culture-positive incisional SSI, prolonged wound drainage, skin necrosis, wound rupture, prolonged wound healing, bleeding, and inflammation.

The time of infection was defined as the date on which the treating surgeon considered the knee to be deeply infected. This date did not always coincide with the time of appearance, as there could be a reluctance to correctly interpret obvious signs of deep infection. In 11 cases, it was not possible to determine the exact date of diagnosis from the hospital records.

The type of infection was determined based on both clinical appearance and timing. An acute haematogenous infection was defined as an infection occurring acutely around a formerly uninfected knee arthroplasty, irrespective of the time from primary arthroplasty until diagnosis of infection. To be classified as an acute haematogenous infection, it had to be clear that there was an interval without signs of infection between the primary arthroplasty and the occurrence of infection. Deep infections that occurred after surgical intervention other than revision or through direct spreading from an adjacent traumatic wound into the joint, or after an arthrocentesis, were classified separately as secondary infections. The remaining infections were classified according to the time of diagnosis into early infections (≤ 3 months from primary arthroplasty), delayed infections (between 3 months and 2 years), and late infections (more than 2 years). In paper I, these remaining infections were even classified as early post-operative infections (≤ 4 weeks) and late infections (> 4 weeks), after those infections diagnosed at a presumed aseptic revision had been classified separately. In 9 cases, based on the existing information, it was not possible to determine the type of infection.

Re-operation prior to the index operation was defined as any operation at the knee joint that did not involve exchange, addition, or removal of a prosthetic component, with the exception of exchange of the tibial insert in conjunction with debridement. In 220 cases (46.0%), re-operations were performed after the diagnosis of a deep infection and before the index operation. Continuous lavage was most common (116 cases), followed by debridement (43 cases, 4 of which included exchange of the tibial insert), arthroscopy (31), wound revision (16), lavage (13), extirpation of a sinus tract (8), and incision and drainage (4). The time from the diagnosis of infection until the re-operation was less than 4 weeks in 205 cases (93.2%).

The index operations were performed at 59 orthopaedics departments throughout Sweden (approximately 1 operation every other year), the first in 1986 (n = 24), and the most recent in 2000 (n = 41). The index operations were categorised

as either one-stage revisions, two-stage revisions, arthrodeses, extractions, above-the-knee amputations, or other operations. Unconventional surgical treatments, such as partial revision or the use of the same components after re-sterilisation, were grouped as other operations.

Antibiotics were widely used, both before and after the diagnosis of a deep infection, but the information in the hospital records was unreliable. Better information was available on the use of antibiotics after the index operation, and in 17 cases a combination including rifampicin was used.

Microbiology. 52 cases were excluded from the study on microbiology (paper II). In 41 cases, no information on microbiological findings was available and in 4 the information was based on culture from a sinus tract, which is regarded as an unreliable type of culture. In 7 cases, the patient record included information on microbiology but the treating doctor had judged that the findings reported had no clinical relevance.

Culture reports were available for study in 288 of the 426 cases. Six were excluded, as the microbiological findings in the culture report had been judged by the treating doctor to be without any clinical relevance and these findings were not in agreement with other information on microbiology reported in the medical record. In 19 cases, the culture was reported negative. Of the 263 cases remaining, 21 had a polymicrobial infection (18 with 2 pathogens and 3 with 3). In one case, two *S. aureus* isolates with different susceptibility patterns each grew in 4 of 5 tissue samples collected during surgery, and in 8 cases two or more strains of CNS were cultured from at least 2 tissue samples each. Of the 296 isolates no susceptibility pattern was reported for 11, leaving 285 isolates for study on antimicrobial susceptibility pattern.

The microbiological findings were based on tissue cultures in 221 cases, on synovial fluid culture (gained either from knee aspiration or during surgical revision) in 165 cases, and on wound culture in 21 cases; in 19 cases, the type of culture was unknown. The decision to include wound cultures was based on the findings of Cuñé and co-workers (Cuñé et al. 2009). Most of the wound cultures were from early infections, and excluding these cases would have led to a bias because of missing information on early infections. It is not known how many patients received antibiotics before sampling for culture.

For species identification we relied on the culture reports from the microbiology departments and statements in the medical records. In some cases, only the type of bacterium (for example "anaerobic Gram-positive coccus") or the genus (for example, *Enterococcus* sp. or *Staphylococcus* sp.) was given. The antibiotic susceptibility reported by the microbiological laboratories as S (sensitive), I (intermediate), or R (resistant) was noted. Isolates of the same bacterial species were not tested against the same antimicrobial agent in all the microbiological laboratories, or throughout the study period. Reported susceptibility to PcV and PcG is reported together as susceptibility to Pc. Staphylococcal isolates were variously tested for susceptibility to oxacillin, dicloxacillin, cloxacillin, or simply isoxazolylpenicillins. An isolate tested against one of these agents was considered to be S, I, or R to isoxazolylpenicillins and those *S. aureus* that were R were called methicillin-resistant (MRSA).

When performing statistical analysis, the pathogens were divided into 9 groups: *S. aureus*, CNS, streptococci, other aerobic Gram-positive bacteria, Gram-negative bacteria, anaerobes, other pathogens, polymicrobial infections, and negative cultures.

Result of treatment. To evaluate the results of treatment, 2 end-points were determined. Firstly, the re-revision rate due to infection was gathered from SKAR. All cases could be followed concerning further revision from the date of index operation – or in the case of a two-stage revision arthroplasty or arthrodesis from the date of stage 2 – until the date of death or until closure of study at the end of 2006. The median follow-up time with respect to re-revision was 7.9 years, with a range from 17 days (due to death early after index operation) to 21.4 years. Re-arthrodesis of an infected arthrodesis and above the knee amputation after an extraction was considered as re-revision, despite that the operation did not include removal of a prosthetic component.

Secondly, the rate of failure to eradicate infection was determined by adding information from the hospital records on failed but not re-revised cases to the re-revision rate. It is difficult to dif-

ferentiate between persistent infection and new infection, especially retrospectively. Furthermore, it can be argued that for the individual patient it is of no importance whether the infection is a persistent or a recurrent one. Thus, all infections diagnosed after the index operation were regarded as a failure to eradicate infection. In some cases, lifelong antibiotics were prescribed, but if no clinical signs of infections were detected these cases were not regarded as failures. The follow-up time with respect to failure to eradicate the infection was calculated as the time from the date of the index operation – or in the case of a two-stage revision arthroplasty or arthrodesis from the date of stage 2 – until date of revision, death, or the latest available information in the medical records. Optimally, the follow-up time should be at least 1 year after conclusion of antibiotic treatment but due to the retrospective nature of this part of the study, this could not always be accomplished. The median follow-up time regarding failure to eradicate the infection was 2.1 years, with a range from 0 to 16.9 years. 80% of the one-stage revisions and 74.7% of the two-stage revisions were followed in this respect for more than a year whereas only 54.9% of the arthrodesis patients and 27.6% and 16.7% of those with extractions and amputations, respectively, could be followed for more than a year. It is possible that patients with persistent infection (that was not revised) were treated at a department other than the one that performed the index operation, and were thereby missed.

Mortality. The 1-year mortality was determined based on information from the Swedish Cause of Death Register (Statistics Sweden).

Prognostic factors. When searching for factors that affected outcome, the analysis was restricted to those cases that were treated with revision arthroplasty in one or two stages. The variables that were tested were: sex, primary diagnosis, age at index operation, Charnley group, the presence of diabetes, the presence of wound complication(s) after primary operation, type of infection, type of pathogen, occurrence of re-operation before the index operation, time from diagnosis to index operation, one- or two-stage revision, year of index operation, the region in which the index operation was performed, and use of rifampicin in antibiotic treatment. For two-stage revision, even the length of the interval between stage 1 and 2 and the state of the joint during the interval was analysed. Those cases with failure to eradicate infection were compared with cases without failure to eradicate infection.

Time trends were studied by dividing the study period into three 5-year periods, with the index operation performed 1986–1990, 1991–1995, or 1996–2000. In paper II, the period was divided depending on the date of culture.

Paper IV

In 114 consecutive cases treated at the department of Orthopaedics, at Lund University Hospital, during 2008 the time of administration of preoperative prophylactic antibiotic in relation to the start of surgery was recorded from the operation report. The information was collected without the involvement or knowledge of the staff who administered the prophylactic antibiotic. According to local guidelines, patients should have the preoperative prophylactic antibiotic 30 minutes before the start of surgery but administration within a time interval from 45 minutes to 15 minutes before start of surgery was regarded as adequate.

The timing of prophylactic antibiotics was not registered in the SKAR before 2009. To search for this information, 300 cases were randomly selected from the 9,238 primary TKAs registered in the SKAR as having been performed during 2007 because of osteoarthritis. The anaesthetic record was requested from the operating unit and 291 reports were received. Four patients had both knees operated on the same day; in 3 cases, the knee selected for study was the first one and in 1 case it was the second. Information on the type and dose of prophylactic antibiotic, as well as the time of administration in relation to the inflation of a tourniquet and to the start of surgery, was searched for in the anaesthetic record. Administration of prophylactic antibiotic more than 45 minutes before the start of surgery was regarded as inadequate because of the short half-life of the most commonly used antibiotics. Administration later than 15 min before the start of surgery was also regarded as inadequate, as in most cases the infusion would not have entered the circulation at the time of incision or inflation of a tourniquet.

Statistics

Paper I. The Chi-square test was used to compare proportions.

Paper II. The Chi-square test was used to evaluate the distribution of microbiological findings. Cuzick's test for trend (a Wilcoxon-type test for trend across a group of three or more independent random samples (Cuzick 1985)) was used to evaluate changes over time in antibiotic susceptibility pattern.

Paper III. The Chi-square test was used to compare proportions. The Kaplan-Meier method was used to calculate the cumulative re-revision rate for infection and the cumulative rate of failure to eradicate infection for those treated with two-stage revision. Censoring events were death and re-revision for reasons other than infection (aseptic revision or above-the-knee amputation due to atherosclerosis). It was assumed that censored cases had the same risk of re-revision or failure to eradicate infection as those that were not censored. This assumption might be untrue, as it is possible that dying and failure to eradicate infection were competing risks.

For statistical evaluation of categorical factors that could be prognostic of outcome, Kaplan-Meier curves were calculated separately for each group and the log rank test used to evaluate whether there were differences in survival. For continuous variables, Cox regression analysis was used.

Paper IV. The 95% confidence interval for proportions was calculated as ± 1.96 standard errors.

For all statistical evaluations, the significance level was set at $p < 0.05$.

The statistical analyses were performed using the software packages PASW Statistics 18 (SPSS, Chicago, IL) and STATA version 11.1 (Stata Corp LP, College Station, TX).

Results / Summary of papers

Paper I: The time and type of deep infection after primary knee arthroplasty

In 478 cases of first-time revisions due to infection, during the years 1986–2000 the time from primary knee arthroplasty until the diagnosis of deep infection was found to range from 3 days to 21.3 years. Two-thirds of the infections (317 cases) were diagnosed within 2 years of primary arthroplasty (Figure 12). Of those that were diagnosed within 2 years, almost half of the cases (143 of 317) were diagnosed within 3 months (Figure 13).

Acute haematogenous infections were found to occur at all times after primary arthroplasty, and could not be classified as a subgroup of late infection. Infections occurring after surgical intervention other than revision or through direct spread from an adjacent traumatic wound into the joint, or after an arthrocentesis, did not fit in to the existing classification systems and were classified separately as secondary infections. Using the classification system proposed by Zimmerli and co-workers, with the modification that acute haematogenous infections could occur at all times and that secondary infections were classified separately, early infection (≤ 3 months) was the most common type of infection (30.3%), followed by delayed infection (between 3 months and 2 years, 28.4%) and acute haematogenous infection (22.0%). Using the classification system proposed by Segawa and co-workers, late (chronic) infection was the most common type of infection (59.9%), followed by acute haematogenous infection (22.0%), and only 52 cases (11.1%) were diagnosed as early postoperative infections; that is, ≤ 4 weeks after primary knee arthroplasty.

In 186 cases, a wound problem was noted during the first 30 postoperative days, before deep infection was diagnosed. The incidence of wound complications varied depending on the type of infection. When using Zimmerli's classification, this varied from 7.4% and 8.7% in those with secondary and acute haematogenous infection, respectively, to 17.2% in those with late infection, and 57.1% and 61.3% in those with delayed and early infection. The most common type of wound complication was wound drainage (n=74), followed by culture-positive superficial surgical site infection (44), skin necrosis (25), wound rupture (21), inflammation (15), prolonged wound healing (5), and bleeding (2).

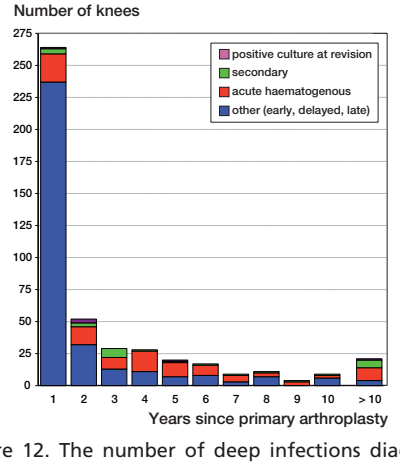

Figure 12. The number of deep infections diagnosed each year after primary knee arthroplasty, shown according to type of infection, in 467 cases that were revised due to infection in Sweden, 1986–2000.

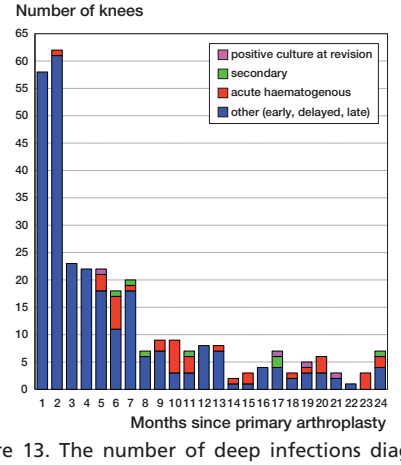

Figure 13. The number of deep infections diagnosed each month during the first 2 years after primary knee arthroplasty, shown according to type of infection, in 317 cases that were revised due to infection in Sweden, 1986–2000.

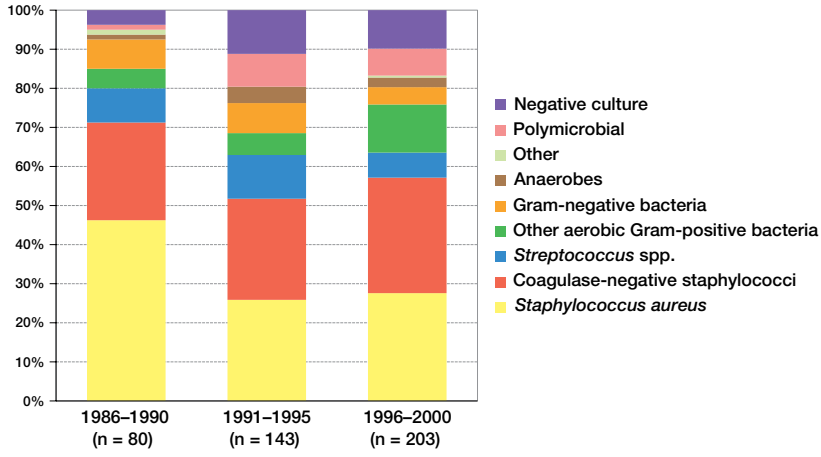

Figure. 14 The microbiological spectrum of infected primary knee arthroplasties surgically revised in Sweden during 1986–2000, divided into 3 periods based on the date of culture.

Paper II: Microbiology of the infected knee arthroplasty: Report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases

The microorganism most commonly found in 426 cases of infected primary knee arthroplasties revised due to infection, during 1986–2000, was *Staphylococcus aureus*, which was the sole causative pathogen in 30.5% of cases, followed by coagulase-negative staphylococcus (CNS), which was the sole pathogen in 27.5% of cases. *Streptococcus* accounted for 8.4% of the infections, *Enterococcus* spp. for 7.7%, Gram-negative bacteria for 6%, and anaerobic bacteria for 2.7%. In 6.3% of cases more than one pathogen was cultured (polymicrobial infections), and in 9.2% the cultures were negative.

The microbiological spectrum varied considerably depending on the type of infection ($p < 0.001$). CNS was the most common pathogen in early, delayed, and late infections (105/229, 35.1%), followed by S. aureus (55/299, 18.4%), whereas S. aureus was the most common pathogen in acute haematogenous infections (67/99, 67.7%), followed by streptococci (19/99, 19.2%) and Gram-negative bacteria (8/99, 8.1%). The most common pathogens in polymicrobial infections were CNS, Gram-negative bacteria and Enterococcus spp.

Only 1 of 84 *S. aureus* isolates (1.2%) tested against isoxazolyl penicillins was resistant (MRSA). Sixty-two of 100 CNS isolates (62%) tested against isoxazolyl penicillins were resistant. Gentamicin resistance was found in 1 of 28 tested isolates of *S. aureus* (4%) and 19/29 tested isolates of CNS (66%).

The microbiology was found to change significantly during the period studied ($p = 0.019$) (Figure 14). The proportion of infections caused by S. aureus decreased from 46.3% during 1986–1990 to 27.6% during 1996–2000. At the same time, the proportion of infections caused by enterococci increased. No enterococcal strains were cultured before 1991 and of the 33 strains cultured, 21 were isolated in 1996 or later.

The reported methicillin resistance among CNS increased during the period studied ($p = 0.002$), with 0/6 reported resistant in 1990 or earlier, 18/31 during 1991–1995, and 45/63 during 1996–2000.

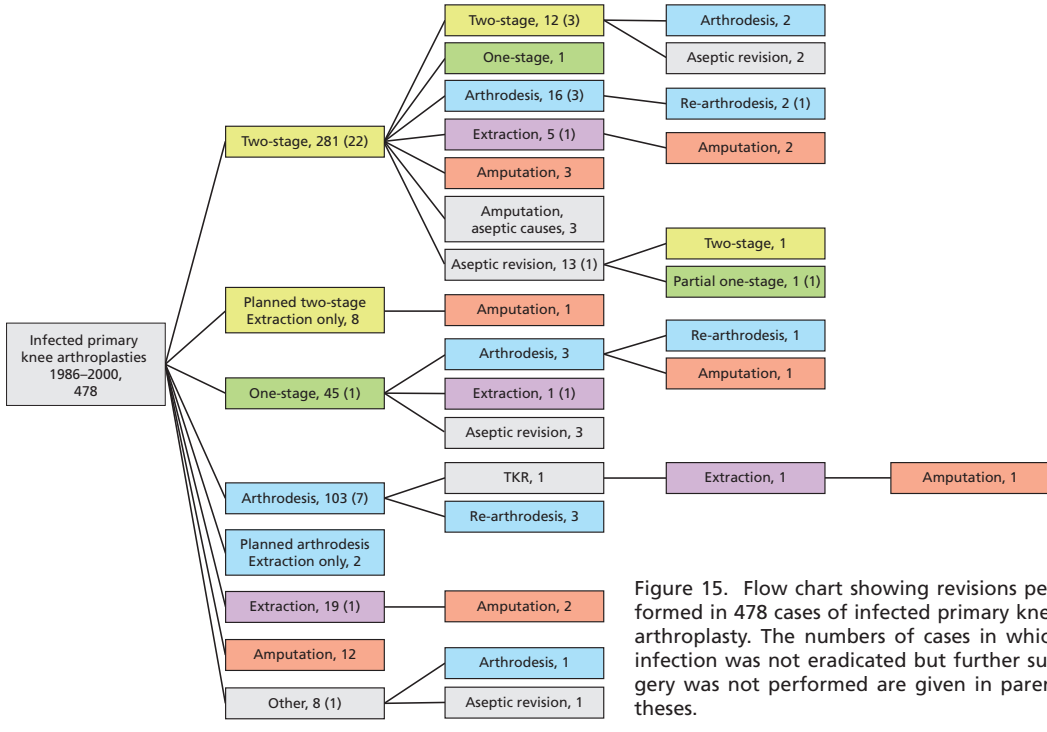

Figure 15. Flow chart showing revisions performed in 478 cases of infected primary knee arthroplasty. The numbers of cases in which infection was not eradicated but further surgery was not performed are given in parentheses.

Paper III: 478 primary knee arthroplasties revised due to infection – a nationwide report

During the period 1986–2000, two-stage revision arthroplasty was the most commonly used surgical treatment for infected primary knee arthroplasty in Sweden (289/478, 60.5%) (Figure 15). There were regional differences in type of treatment. The highest proportion of patients treated with revision arthroplasty (one- or two-stage) was in the western region (78%), and the lowest in the northern region (61%). The highest proportion of patients treated with an arthrodesis was in the northern region (33%), and the lowest was in the western region (12%). 40% of the one-stage revisions were performed in the southern region. The proportion of patients undergoing revision arthroplasty increased from 59.6% in the period 1986–1990 to 75.3% during 1995–2000, and the proportion of patients having an arthrodesis decreased from 27.3% in 1986–1990 to 19.5% in 1995–2000.

After a two-stage revision arthroplasty, the cumulative re-revision rate because of infection

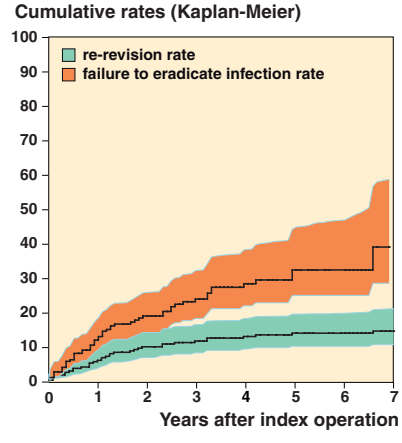

Figure 16. The cumulative re-revision rate and rate of failure to eradicate infection after 281 two-stage revision arthroplasties performed in Sweden, 1986–2000.

was 9.4% (95% CI 6.5–13.5) at 2 years and 12.7% (95% CI 9.2–17.8) at 5 years. The cumulative rate of failure to eradicate infection was 17.8% (95% CI 13.3–24.0) at 2 years and 27.5% (95% CI 21.3–38.3) at 5 years (Figure 16). Arthrodesis was the most common surgical method used when re-revising an infected knee arthroplasty (Figure 15).

The only factor that was found to be predictive of failure to eradicate infection after a revision arthroplasty (one- or two-stage) was a history of wound complication after the primary operation and before deep infection was diagnosed (p=0.005). The risk of failure to eradicate infection was doubled for those with a history of wound complication after primary arthroplasty compared to those who did not have a history of wound complication (RR=2.04, 95% CI 1.23–3.39). Of the 34 cases with wound complication and where there was a failure to eradicate infection, 31 were early or delayed infections.

In 59 of the 281 two-stage revisions that were completed, and in 5 of the 45 one-stage revisions, infection was not eradicated. The difference was not significant (p=0.150), but it is questionable whether comparison should be made because of differences in selection.

A spacer block made of antibiotic-loaded PMMA was the most commonly used method for local antibiotic treatment and stabilisation of the joint during the interval between stage 1 and stage 2. Using both PMMA beads and a spacer gave a lower rate of failure to eradicate infection, but compared to spacer the difference was not statistically significant (p=0.123).

The most commonly used technique to accomplish an arthrodesis was external fixation, which was used in 79 cases, 38 of which were done in a two-stage manner. An intramedullary rod was used in 21 cases, 17 of which were done in 2 stages. In 2 cases, the joint was stabilised with pins (one-stage), and in 1 case it was stabilised with a plate and screws (two-stage).

The 1-year mortality for those patients treated with extraction of the implant or above-the-knee amputation was high.

Paper IV: Inadequate timing of prophylactic antibiotics in orthopedic surgery. We can do better

As the effect of prophylactic antibiotics is related to the timing of administration, it is important to follow how the routines with preoperative prophylactic antibiotics are working. A small study at the Department of Orthopaedics, Lund University Hospital, initiated by a local strategic program against antibiotic resistance, signalled that the timing of administration was inadequate. To verify these results and to test the hypothesis that the timing was inadequate even at other departments, a larger study was conducted in Lund, and 291 cases randomly selected from the SKAR – from the 9,238 primary TKAs reported to have been performed because of OA during 2007 – were studied .

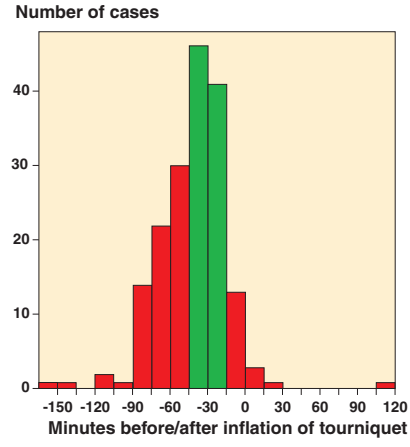

Figure 17. The timing of administration of prophylactic antibiotic in relation to the inflation of a tourniquet in 176 cases of primary TKA. Zero represents the start of surgery. The green bars correspond to acceptable timing.

Of the 114 patients studied in Lund, only 51 (45%, 95% CI: 36–54%) received the first antibiotic dose of antibiotic between 45 and 15 minutes before the start of surgery. In 22 cases (19%), surgery was started at the same time or before administration of prophylactic antibiotic. In the material from the SKAR, the time of administration of the first doses of antibiotic prophylaxis could be ascertained from the anaesthetic record in 198 cases. Only 113 patients (57%, CI: 50–64%) received the antibiotic between 45 and 15 minutes before the start of surgery. The mean time was 41 minutes, with a range from 105 minutes before the start of operation to 120 minutes after the start. In 176 cases, it was possible to read the time from administration of prophylactic antibiotic until the time of inflation of a tourniquet. Only 94 (53%, CI: 46–61%) received antibiotics between 45 and 15 minutes before the tourniquet was applied (Figure 17). The mean time was 40 minutes, with a range

from 153 minutes before the inflation of a tourniquet to 120 minutes after inflation.

In 2 of the 4 bilaterally operated patients, no additional antibiotic was given before the start of surgery on the second knee.

Information on type of antibiotic used was available in 247 cases (85%), and of these 89% had received cloxacillin, 9% clindamycin, and 2% cefuroxime. The most common dose of cloxacillin was 2 g (158/212 patients, 75%).

Discussion

Deep infection after a knee arthroplasty is a demanding and growing problem (Kurtz et al. 2007). In papers I–III, a large number of primary knee arthroplasties that were surgically revised due to an infection, during the years 1986–2000, were identified by searching the Swedish Knee Arthroplasty Register (SKAR). The information was used to determine the timing and type of infection, the microbiology and antimicrobial resistance pattern, and the type of treatment and results thereof. The strength of the study is that it covered all revisions performed, irrespective of type of hospital, type of infection, or type of treatment. In paper IV, a specific and important part of the preventive measures was studied – i.e. the timing of administration of the first dose of prophylactic antibiotic.

Limitations of the study

The major drawback of the study is that not all infected knee arthroplasties were included. An unknown number of patients were treated without revision of the prosthetic components, and were thereby not reported to the register. Those who were not included may have been the frail or elderly patients, those who refused surgery, those who were treated with suppressive antibiotics, or those with soft tissue operation only. It is not possible to predict the effect of these cases on the overall result. In addition, it is probable that infections caused by low-virulence organisms were (to an unknown extent) not diagnosed as being septic during revision and were therefore not reported. Data on some of the variables were collected retrospectively, which could have affected the reliability. The information gathered was not complete in all cases, and some data were less available during the first years of the study. In addition, no information was available on several factors that may have affected the outcome, with the state of the soft tissues around the knee, complete information on co-morbidities, and smoking habits probably being the most important ones.

Timing and type of infection

There have been relatively few reports involving all infected knee arthroplasties, and not only a subgroup of patients (Walker and Schurman 1984, Grogan et al. 1986, Bengtson et al. 1989, Bengtson and Knutson 1991, Rasul et al. 1991, McPherson et al. 1999, Segawa et al. 1999, Peersman et al. 2001, Husted and Toftgaard Jensen 2002, Laffer et al. 2006, Pulido et al. 2008). In these studies, the onset of infection was reported to be within 3 months of surgery in 29–46% of cases and within 4 weeks in 3–48% of cases. The proportion of haematogenous infections varied from 6% to 49%. There are several methodological differences between the studies, which is why comparisons should be done with caution. The largest study, involving 357 cases operated during 1975–1985, was an earlier study from the SKAR where 46.5% of the infections were diagnosed within 3 months of primary arthroplasty; 25% were reported to be of haematogenous origin, and in 40% of cases the primary diagnosis was RA (Bengtson and Knutson 1991). Today, the overwhelming majority of patients who undergo knee arthroplasty have OA (Figure 1), and as the most common type of infection in OA patients was early infection, this type of infection is probably even more common now than during the study period.

As there is no clear evidence for the statement that infections with a duration of less than 4 weeks can be treated with debridement, there is no reason to classify the infections as early postoperative (≤ 4 weeks) and late (>4 weeks). Classification of infections as early (≤3 months after the primary arthroplasty) and delayed (3 months to 2 years) highlights the pathogenesis and the general belief that most infections are acquired during or shortly after surgery, but may not be detected until later. The high incidence of wound problems in those with delayed infection supports this view. Wound complication is a well known risk factor for later diagnosis of deep infection (Berbari et al. 1998, Abudu et al. 2002, Saleh et al. 2002, Phillips et al. 2006, Galat et al. 2009), but surprisingly little

guidance can be found in the literature regarding optimal treatment (Vince and Abdeen 2006) and the results of treatment (Galat et al. 2009).

Acute haematogenous infections should be classified separately, irrespective of the length of time from primary operation. Furthermore, we defined a group of secondary infections that should be classified separately.

Microbiology

CNS was the most prevalent pathogen in the early and delayed infections. Infections caused by CNS often present with subtle clinical signs and can often be suppressed easily, but not eradicated, with antibiotics. A high level of awareness is needed for identification and for timely, resolute treatment.

The number of studies that have described the microbiology in infected knee arthroplasties is limited. In a study of 121 patients who were revised because of an infected knee arthroplasty at an English hospital during the period 1994–2008, CNS caused 49% of the infections, *S. aureus* 13%, *E. coli* 7%, *Enterococcus faecalis* 6%, and other bacteria 25% (Nickinson et al. 2010). Information on type of infection was not provided in the paper. In a study on 84 cases of knee arthroplasty, re-operated at either of two hospitals in the USA during 1991–2003, *S. epidermidis* caused 36% of the infections, *S. aureus* 32%, *Streptococcus* spp. 11%, *Enterococcus* spp. 7%, *E. coli* 2%, *Pseudomonas aeruginosa* 2%, *Corynebacterium* spp. 7%, and other bacteria 7% (Fulkerson et al. 2006). Of those 8 infections that occurred within 4 weeks of surgery, 4 were caused by *S. aureus.*

The microbiological findings in acute haematogenous infections differed significantly from the findings in early, delayed, and late infections, *S. aureus* being the dominating pathogen. Identifying the source of an acute haematogenous infection is in many cases a difficult task and in a retrospective study even more difficult. In the few cases in which origin could be identified, leg or foot ulcer was the most common source. There is little information on haematogenous infections in the literature, but Fulkerson and co-workers report that haematogenous infections accounted for 17.8% of infected knee arthroplasties and *S. aureus* was the infecting pathogen in 6/15 (40%) (Fulkerson et al. 2006).

The proportion of polymicrobial infections was in accordance with that in other studies (Peersman G 2001, Pulido et al. 2008), and as described earlier, polymicrobial infections were most common in early infections (Marculescu and Cantey 2008).

Antibiotic susceptibility

The testing of anti-microbial susceptibility was not standardised, and during the study period, minimum inhibitory concentration (MIC) breakpoints for several species and antibiotics were changed. As a result of this, caution is required when interpreting the results of antibiotic susceptibility.

The prevalence of methicillin-resistant *S. aureus* (MRSA) was very low but consistent with the generally low prevalence of MRSA in Sweden (Stenhem et al. 2006).

Only 9 of 29 CNS isolates tested were sensitive to gentamicin, which is in accordance with what has previously been reported in infected hip arthroplasty (Hope et al. 1989). The gentamicin resistance among CNS strains must be considered in revision of an infected knee arthroplasty, and other antibiotic(s) added to the bone cement used in contemporary spacers and at re-arthroplasty.

The microbiological spectrum changed over time, with a decrease in the proportion of infections caused by *S. aureus* after 1990. There was also a change in primary diagnosis, with an increase in OA and decrease of RA. Even though the immune system in rheumatoid patients is affected in a complicated manner, both by the disease and its treatment, the decrease in infections caused by *S. aureus* cannot, with our current knowledge, be explained by the changes in primary diagnosis. Another factor, that unfortunately could not be studied, is the use of antibiotic-impregnated bone cement. Data from the Swedish Hip Arthroplasty Register show that the use of antibiotic-impregnated bone cement became widespread in hip arthroplasty at the beginning of the 1990s (SHPR 2003), and it is likely that the same applies to knee arthroplasty. It could be hypothesised that the use of antibiotics in bone cement had greater effect on *S. aureus* than on CNS, but it is very difficult to evaluate separately

the effects of the various prophylactic measures that have been introduced in orthopaedic surgery. The microbiology in infected knee arthroplasties has to be examined in the context of the overall incidence. In previous reports from the SKAR, the cumulative revision rate (CRR) due to infection has been shown to have decreased from 2.7% during 1976–1985 to 1.1% during 1986–2000 (Figure 2). With the described decrease in infections caused by *S. aureus,* CNS is now the most important pathogen in infected knee arthroplasty. The methicillin resistance among CNS strains found in infected cases increased. Further studies are required to determine the present status as well as the prevalence of methicillin-resistant CNS in patients at admission and in the hospital environment. Betalactams continue to be the best choice of systemic antibiotic prophylaxis, but there is good reason to remind all the personnel involved about preventive measures other than antibiotics that have been shown to be effective – and are especially important in the case of CNS. The observed increase in infections caused by enterococci, especially during the first post-operative period, is a matter of concern and requires further study.

Type of treatment

The existing guidelines for choice of surgical treatment in infected knee arthroplasty are largely based on empirical findings. The factors to be considered when choosing the type of treatment for the individual patient are: the duration of symptoms, the general health of the patient, the condition of the soft tissues and the implant, and bacteriology (Zimmerli et al. 2004, Leone and Hanssen 2005). In practice, even other factors such as local tradition, the skill and experience of the orthopaedic surgeon, and the availability of expert knowledge in microbiology and infectious diseases can affect the choice of treatment, and these factors may explain the regional differences found in the choice of treatment. It is difficult to compare the distribution between different treatment alternatives found in our study with that in other studies, due to the limited number of reports on all infected knee arthroplasties treated. In a previous Swedish study from 1973–1986, the proportion of patients treated with revision arthroplasty was 45.5% and the proportion treated with an arthrodesis was 38.6% (Bengtson et al. 1989). In more recent studies, the proportion of surgically revised patients treated with a revision arthroplasty has been reported to be in the 68–90% range, and the proportion treated with an arthrodesis to be in the 10–16% range (Segawa et al. 1999, Husted and Toftgaard Jensen 2002, Laffer et al. 2006, Kosters et al. 2009). There appear to have been many arthrodeses in the present study, but it must be kept in mind that there were more rheumatoid patients during the earlier years of the study; they may have had poorer bone stock and inferior quality of the soft tissues. We plan to analyse the results of arthrodeses in a future study.

There are many unanswered questions with regard to the best possible treatment, and good results have been reported with the use of treatment strategies that divide considerably from those in the present algorithms. For example, two-stage revisions have been performed without the use of prolonged antibiotic treatment and the infection reported to be successfully eradicated in 34/38 cases (89%) (Hoad-Reddick et al. 2005). In another study, 18 patients with MRSA infected knee arthroplasties were treated with a one-stage uncemented revision, followed by intra-articular administration of vancomycin for 6 weeks and only 24 hours of intravenous antibiotics. At a mean follow-up of 62 months the infection was controlled in all but one patient (Whiteside et al. 2010).

The results of treatment

The crude rate of failure to eradicate infection of 21% found in our study after a two-stage revision arthroplasty is in line with publications reporting the poorest results (Jämsen et al. 2009b). Survival analysis, which takes into account that during follow-up some patients die or are revised for reasons other than infection, revealed still higher failure rates (27.5% at 5 years). It can be questioned, however, whether the patients reported in published studies are representative of the whole group of patients treated for infected knee arthroplasty. Probably our results better reflect the everyday reality that most patients and orthopaedic surgeons

are faced with. To improve the results, it appears reasonable to suggest centralisation of treatment to fewer centres. The failure rate after one-stage revision arthroplasty is in accordance with earlier reports, but differences in selection make comparisons with previous studies or with two-stage revision meaningless.

The best results were obtained with two-stage revision arthroplasty when an antibiotic-loaded PMMA spacer and antibiotic-loaded PMMA beads were left in the joint during the interval between stages one and two, even though the difference was not statistically significant. Beads have elution characteristics that differ from those of spacers, which may be beneficial (Walenkamp 2001, Anagnostakos et al. 2009).

Mortality

According to data from the SKAR, the 1-year mortality after a primary knee arthroplasty performed during 1989–2008 was 1.4%. The substantially higher mortality found after arthrodesis, extraction, and amputation probably reflects the poorer medical condition of the patients treated by these methods.

Prognostic factors for failure to eradicate infection

A history of wound complication after the primary knee arthroplasty and before the diagnosis of deep infection was the only factor that was found to be predictive of failure to eradicate infection after a revision arthroplasty. It is not clear how a delay in correct diagnosis can affect the result of treatment. The use of antibiotics in patients who had wound complications was extensive, but the exact magnitude was unfortunately impossible to measure accurately retrospectively. It is possible that prolonged antibiotic treatment, with retained and undebrided implant, enhances the development of antibiotic resistance and thereby makes the infection more difficult to treat when revised. To our knowledge, this has not been described before and further studies are needed. Recently, poorer outcome has been reported after revision arthroplasty in cases of failed open debridement and irrigation (Sherrell et al. 2010, Gardner et al. 2010).

It was a disappointment not be able to reveal any other prognostic factors, but even though the present cohort included a large number of patients, it was heterogeneous and many orthopaedic surgeons with varying degrees of experience were involved. Furthermore, there was variability regarding the possibility of consulting infectious disease and microbiology specialists. Prospective collection of data, including better estimation of co-morbidities, is needed.

Timing of antibiotics

The number of patients in our study who received the first dose of antibiotic at a suboptimal time was alarming, and raises concerns about other aspects of prophylactic measures. It was recently shown in a non-randomised study that the use of a simple surgical safety check-list reduced morbidity and mortality. The administration of antibiotics within 60 min before incision improved from 56% to 83% by use of the safety list, and the surgical site infection rate was reduced by almost 50% ($p < 0.001$) (Haynes et al. 2009). The use of a check-list is recommended.

The half-life of cloxacillin is relatively short (30 minutes), with cefuroxim and clindamycin having somewhat longer half-lives (66 and 155 minutes, respectively). If the antibiotic is given too early before the start of surgery, it is not certain that the concentration of antibiotic in the tissue will be high enough throughout the whole operation. Thus, one could consider whether or not all patients for whom the actual surgical procedure takes more than 1 hour should have a new infusion, starting just before the tourniquet is released. This is also what the AAOS has recommended in its recent document on infection prophylaxis (Prokuski 2008). The document states that at twice the half-life of the selected antibiotic (counting from the first injection), a repeat dose should be given. In knee arthroplasty surgery, this very often coincides with the release of the tourniquet. If antibiotic is given too late, the antibiotic may not reach the tissue at the time of surgery. This is especially important when a tourniquet is used during the operation.

The future

Antimicrobial resistance is a growing problem. The result of treatment appears to be poorer when the infection is caused by methicillin resistant bacteria (Kilgus et al. 2002, Bradbury et al. 2009, Kurd et al. 2010) and in areas with high prevalence of methicillin resistant bacteria vancomycin has been recommended as a prophylactic antibiotic (Meehan et al. 2009). Prophylactic methods other than antibiotics, which can reduce the number of infections, will probably become increasingly important. Good effect of decolonisation with chlorhexidine, either as soap or impregnated clothes, has recently been reported (Bode et al. 2010, Johnson et al. 2010). It is likely that increased attention will be paid to the quality of air in the operation theatre as well as to strict adhesion to hygiene routines in hospitals.

There is ongoing experimental work on coating of implants with antibiotics (Lawson et al. 2010, Smith et al. 2010). With better understanding of the mechanism controlling the formation of a biofilm it may become possible to disturb the biofilm formation and thereby reduce the risk of infection and improve the results of treatment of a manifest infection (Hoiby et al. 2010).

Conclusions

- Of the 478 first-time revisions performed due to infection after a primary knee arthroplasty in Sweden 1986–2000, 30% were diagnosed within 3 months from primary operation and two-thirds were diagnosed within 2 years. In these cases, a wound complication was frequently noted after the primary arthroplasty but before the diagnosis of deep infection. Acute haematogenous infections, which accounted for 22% of cases, were found to occur at all times after primary arthroplasty and to be more common in patients with RA than in those with OA. Awareness of the fact that most infections arise early and are associated with wound complications should encourage use of judicious postoperative care and could lead to earlier diagnosis and treatment.
- *S. aureus* was the most commonly found microorganism in the 426 cases that were available for microbiological analysis. During the study period, the proportion of infections caused by *S. aureus* decreased however, and during the last 5-year period CNS was the most commonly found microorganism. CNS was even the most commonly found microorganism in early and delayed infections. MRSA was found in only 1 case, whereas increasing methicillin resistance was noted in the CNS isolates. Gentamicin resistance was common in CNS, which has to be considered in revision surgery – at least when the revision is performed due to infection – as antibiotic other than gentamicin should be added to the bone cement.
- A two-stage revision knee arthroplasty was the surgical method chosen in 60% of the 478 cases that were revised for the first time due to an infection during the years 1986–1990. Another 9% had a one-stage revision. Almost 30% were treated with the poorer functional alternatives: arthrodesis, extraction of the implant, or above-the-knee amputation. There were regional differences in the type of surgical treatment chosen, and the average number of cases treated at each orthopaedics department was 1 every other year. By centralising the treatment to units with specialists in orthopaedics and infectious diseases working in a team, every patient could be offered the most optimal treatment available.
- After a two-stage revision arthroplasty, only half of those with failure to eradicate infection were re-revised, the cumulative re-revision rate at 2 years being 9.4% and the cumulative rate of failure to eradicate infection being 17.8%. These figures are in line with the poorest results reported in other studies, which indicates that there is room for improvement. The only factor that was found to be predictive of failure to eradicate the infection was a history of wound complication(s) after the primary operation, before the diagnosis of infection. This implies that every surgeon performing knee arthroplasties has to be capable of taking adequate care of wound complications.
- The time of administration of the first dose of prophylactic antibiotic was suboptimal in 55% of the cases studied at Lund University Hospital, and in 47% of the cases randomly selected from the SKAR. To bring about a change for the better, it is suggested that the WHO's checklist should be used at all operations, and that the timing of antibiotic administration be reviewed regularly at all departments.

Populärvetenskaplig sammanfattning

Vid en knäprotesoperation ersätts ledytorna i knäet med en protes gjord av metall och plast. Den vanligaste orsaken till denna operation är artros (ledsvikt). Antalet knäprotesoperationer ökar stadigt och 2009 utfördes 12,700 förstagångsoperationer i Sverige. Resultaten är överlag goda men en allvarlig komplikation som drabbar mellan 1 och 2% av patienterna är bakterieinfektion i leden. Om infektionen upptäcks tidigt kan den behandlas med upprensning i leden och antibiotika men annars måste protesen avlägsnas. En ny protes kan sedan sättas in, antingen vid samma operation (en-stegsrevision) eller efter en protesfri period då patienten behandlats med antibiotika (två-stegsrevision). I vissa fall leder behandling av infektionen till steloperation och enstaka gånger till slinkled (led utan protes) eller amputation. Sedan 1975 har Svenska Knäprotesregistret (SKAR) samlat information om knäprotesoperationer utförda i Sverige och denna databas har använts för att i detalj granska 478 fall som under åren 1986 till 2000 genomgick en knäprotesrevision på grund av infektion. En revision är en omoperation där protesdelar insättes, bytes eller borttages.

Studien visade att i 30% av fallen hade infektionen bekräftats inom 3 månader från primäroperationen och att två tredjedelar av infektionerna hade bekräftats inom 2 år. Sårproblem efter primär operationen var vanligt förekommande bland dessa patienter. För att upptäcka infektioner tidigt är noggrann uppföljning under den första tiden efter operation viktig och infektion måste misstänkas i de fall där sårproblem föreligger. Drygt 20% av infektionerna uppstod efter att bakterier tagit sig via blodbanan till leden. Denna typ av infektion (hematogen infektion) var vanligare hos patienter med ledgångsreumatism än hos de med ledsvikt.

Infektionerna orsakades oftast av stafylokocker, som är bakterier som normalt finns på huden. Under de första åren som studerades var Stafylococcus aureus (den gula stafylokocken) vanligast, medan koagulas-negativa stafylokocker (KNS, den vita stafylokocken) orsakade flest infektioner under de senare åren. I enbart 1 fall orsakades infektionen av meticillinresistent stafylococcus aureus (MRSA). Resistens bland KNS mot meticillin ökade under studietiden och närmare undersökningar behövs för att ta reda på hur vanligt det är att patienter inför knäprotesoperation bär på meticillinresistenta KNS. Bland KNS var resistens mot gentamicin, vilket är det antibiotikum som blandas i bencement för att minska risken för infektion, också vanlig och det måste ortopeder ta hänsyn till vid revisioner utförda på grund av infektion.

Den vanligaste behandlingsmetoden var två-stegsrevision (60%) och ytterligare 9% fick en ny knäled genom en-stegsrevision. Nästan 30% behandlades med steloperation, slinkled eller amputation. Det var regionala skillnader i val av behandling och de flesta ortopedkliniker behandlade mycket få fall. Det föreslås att knäprotesrevisioner på grund av infektion centraliseras till enheter där ortopeder och infektionsläkare tillsammans styr behandlingen.

Två år efter två-stegsrevisionen hade 17.8% misslyckats med att bli av med infektionen. Vid denna tidpunkt hade 9.4% reviderats ytterligare en gång på grund av infektion (räknat med Kaplan-Meiers metod). Dessa resultat motsvarar de sämsta resultaten som har presenterats tidigare, men jämförelse försvåras av att tidigare studier ofta kommer från högspecialiserade enheter. Den enda faktorn som uppvisade ett samband med senare misslyckande i att bota infektion var förekomsten av sårproblem efter primäroperationen. Detta understryker ytterligare vikten av ett adekvat omhändertagande av patienter med sårproblem.

I en separat studie granskades vid vilken tidpunkt den första dosen av förebyggande antibiotikum gavs. För att uppnå den bästa effekten av antibiotika rekommenderas att första dosen ges inom 45 till 15 minuter före operationsstart. Bland patienter opererade på Universitetssjukhuset i Lund fick 55% den första dosen utanför denna tidsrymd. Bland ett slumpmässigt urval patienter som registrerats i SKAR i samband med en knäprotesoperation fick 47% den första dosen antibiotikum utanför denna tidsrymd. Användning av en checklista, framtagen av världshälsoorganisationen WHO, kan medföra en förbättring och rekommenderas.

Yfirlit á íslensku

Við liðskiptaaðgerð á hné er liðflötum hnésins skipt út fyrir gervilið úr málmi og plasti. Slitgigt er algengasta orsök aðgerðar. Liðskiptaaðgerðum á hné fjölgar stöðugt og í Svíþjóð nam fjöldi aðgerða 12,700 árið 2009. Árangur aðgerðar er almennt góður, en þó verða 1-2% sjúklinga fyrir því að fá bakteríusýkingu í liðinn. Sýkingu sem greinist snemma má lækna með því að hreinsa og skola liðinn og gefa sýklalyf, en að öðrum kosti þarf að fjarlægja gerviliðinn. Hægt er að setja inn nýjan gervilið, annað hvort við sömu aðgerð (eins-þreps enduraðgerð) eða eftir að hnéð hefur verið án gerviliðar um tíma og sjúklingurinn fengið sýklalyf (tveggja-þrepa aðgerð). Í vissum tilvikum leiðir sýkingin til staurliðsaðgerðar, varanlegrar fjarlægingar gerviliðsins eða aflimunar. Sænska hnégerviliðaskráin (Svenska knäprotesregistret) hefur frá 1975 safnað upplýsingum um liðskiptaaðgerðir á hné sem framkvæmdar eru í Svíþjóð. Úr skránni voru fengin 478 tilfelli sem á árunum 1986–2000 höfðu gengist undir aðgerð þar sem gerviliður var fjarlægður eða skipt út vegna sýkingar og þau rannsökuð ítarlega.

Í 30% tilvika greindist sýkingin innan þriggja mánaða frá fyrstu aðgerð og tveir þriðju hlutar sýkinganna höfðu greinst innan tveggja ára. Í þessum hópi voru vandamál tengd skurðsári mjög algeng. Mælt er með góðu eftirliti með sjúklingum fyrst eftir aðgerð og að tekið sé á vandamálum tengdum skurðsári af ákveðni. Rúmlega 20% sýkinganna voru blóðbornar, það er að bakteríur dreifðust með blóði í liðinn. Þessi tegund sýkingar var algengari hjá liðagigtarsjúklingum en slitgigtarsjúklingum.

Sýkingin var oftast af völdum stafýlókokka, sem eru bakteríur sem tilheyra eðlilegri húðflóru. Fyrstu ár rannsóknarinnar var Stafýlókokkus aureus (guli stafýlókokkurinn) algengastur en þau síðustu kóagúlasaneikvæðir stafýlókokkar (KNS, hvíti stafýlókokkurinn). Í einungis einu tilfelli orsakaði methisillín-ónæmur Stafýlokokkus aureus (MÓSA) sýkingu. Ónæmi meðal KNS gegn methisillíni jókst á tímabilinu og nánari rannsókna er þörf til að ganga úr skugga um hversu algengir methisillín-ónæmir KNS eru á húð þeirra sem gangast undir liðskiptaaðagerð. Ónæmi gegn gentamicin var einnig útbreytt meðal KNS, en gentamicin er það sýklalyf sem blandað er í beinsement til að minnka líkur á sýkingu, og þurfa læknar að taka tillit til þessa við enduraðgerðir vegna sýkingar.

Algengasta skurðmeðferðin var tveggja-þrepa enduraðgerð (60%) og 9% til viðbótar fengu nýjan gervilið við eins-þreps aðgerð. Tæplega 30% sjúklinga voru meðhöndlaðir með staurliðsaðgerð, varanlegri fjarlægingu gerviliðs eða aflimun. Flest sjúkrahús meðhöndluðu fáa sjúklinga og svæðisbundinn munur var á hvaða meðferð var valin. Lagt er til að enduraðgerðir vegna sýkinga í hnégerviliðum fari fram á sjúkrahúsum þar sem bæklunarlæknir og smitsjúkdómasérfræðingur starfa náið saman.

Tveimur árum eftir tveggja-þrepa enduraðgerð höfðu 17.8% sýnt merki þess að sýking væri í liðnum. Önnur enduraðgerð vegna sýkingar hafði verið framkvæmd hjá 9.4%. Þessi árangur er með þeim lakari sem kynntur hefur verið, en samanburður er erfiður þar sem fyrri rannsóknir hafa flestar verið gerðar við sérhæfðar stofnanir. Eina breytan sem reyndist hafa forspárgildi fyrir áframhaldandi sýkingu í liðnum eftir enduraðgerð var vandamál tengt skurðsári eftir fyrstu aðgerð. Þetta undirstrikar enn frekar mikilvægi þess að sinna þessum vandamálum vel.

Í sérstakri rannsókn var skoðað hversu mörgum mínútum áður en aðgerð hófst sjúklingar fengu fyrsta skammt fyrirbyggjandi sýklalyfjagjafar, en mælt er með að fyrsti skammtur sé gefinn 45 til 15 mínútum fyrir aðgerð. Meðal sjúklinga sem gengust undir aðgerð við Háskólasjúkrahúsið í Lundi reyndist tímasetning fyrstu sýklalyfjagjafar vera utan réttra tímamarka í 55% tilvika. Í tilviljunarkenndu úrtaki sjúklinga úr sænsku hnégerviliðaskránni reyndust 47% hafa fengið fyrsta skammtin utan réttra tímamarka. Til úrbóta er mælt með notkun gátlista, sem gefinn hefur verið út af Alþjóðaheilbrigðismálastofnuninni (WHO).

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