PERSPECTIVES ON TREATMENT AND OUTCOME OF CHRONIC PERIPROSTHETIC HIP JOINT INFECTION

PhD thesis

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Preface

This PhD thesis is based on clinical epidemiological studies carried out while employed as a PhD student at the University of Aarhus between 2009 to 2015.
This employment was only possible due to a co-financed scholarship between Orthopaedic Research Aarhus, Aarhus University Hospital, and The Lundbeckfoundation centre for fast-track hip and knee surgery initiated in 2008 by Professor Henrik Kehlet and Professor Kjeld Søballe. The research in this thesis has also kindly been supported by The Lundbeckfoundation centre for fast-track hip and knee surgery and the Elisabeth og Karl Ejnar Nis-Hanssens Mindelegat.

My deepest gratitude goes to my supervisors; Professor Kjeld Søballe and Professor Anders Troelsen, for giving me the opportunity to grow as a person and develop as a scientist at this most enjoyable field of orthopaedic research. We still have a lot to do.

Many departments of orthopaedic surgery are involved in the Lundbeckfoundation centre for fast-track hip and knee surgery, and the studies in this thesis would not have been possible, without the full dedication of surgeons and associated staff, at each of these departments, to whom I am forever grateful for allowing me to enter their spheres.

So much time, and effort, has been used in the past 6+ years, reaching this exact point, the fabrication of this thesis.
And all this had not been possible, if not for the help from Inger, Aksel, Eva-Marie, Malene, the rest of my family, friends and colleagues. Sometimes enduring long periods of coaching, sometimes just a simple word at the right time, to make it all fit perfectly together.
This preface do not allow for a thorough enumeration. But I hope, you all appreciate the fact, that I know who you are, and you know who you are, and I will never forget.
Thank you all.

This thesis, all the work behind, and all the work ahead, would be completely meaningless to me, was it not for the three brightest stars in my life: my children Alexander, Emma-Marie and Malte.

Jeppe Lange
Aarhus 2015

This thesis is based on the following papers:

I. Lange J, Troelsen A, Thomsen RW, Soballe K. Chronic infections in hip arthroplasties: comparing risk of reinfection following one-stage and two-stage revision: a systematic review and meta-analysis. Clin Epidemiol 2012;4:57-73.

II. Lange J, Pedersen AB, Troelsen A, Søballe K. Do hip prosthesis related infection codes in administrative discharge registers correctly classify periprosthetic hip joint infection? Hip Int 2015 (*in press*)

III. Lange J, Troelsen A, Pedersen AB, Søballe K. Outcome of chronic periprosthetic hip joint infection. Competing risk analysis in a multicenter historical cohort with minimum 5-year follow-up. *Submitted for publication February 2015*

The papers in the thesis will be referred to by their Roman numeral.

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Abbreviations

In alphabetic order

ASA:	American Society of Anesthesiologists
BMI:	Body Mass Index
CCS:	Charlson Comorbidity Severity index
CI:	Confidence Interval
CPR:	Civil Personal Registration
ICD-10:	World Health Organization's International Classification of Disease 10th revision
iv:	intravenous
IQR:	Inter Quartile Range
MSIS:	American Musculoskeletal Infection Society
NCSP:	Nordic Medico-Statistical Committee classification of surgical procedures
PCR:	Polymerase Chain Reaction
PMMA:	polymethylmethacrylate (*bone cement*)
po:	per oral
PROM:	Patient Reported Outcome Measures
USA:	United States of America
USD:	United State Dollars

English Summary

Periprosthetic hip joint infection has always been a devastating complication following implantation of a hip joint replacement. Important perspectives on the treatment and outcome of this complication continues to be evaluated, but the overall lack of knowledge is still profound. There is an urgent need for improvement in our knowledge on chronic periprosthetic hip joint infections.
The overall aim of this thesis was to evaluate perspectives pertaining to treatment and outcome of chronic periprosthetic hip joint infection.

We performed a systematic review and meta-analysis (I) on the risk of reinfection following one-stage and two-stage revisions for chronic periprosthetic hip joint infection. Two-stage revision is by many regarded as the gold standard in treatment of chronic periprosthetic hip joint infection. We found a slight increased risk of re-infection following one-stage revision, although not clinical significant interpreted in light of the included low-quality studies, and overlapping confidence intervals. The study underscores the need for improvement in reporting and collection of high quality data.
We evaluated if single-source administrative register data could be of use in research on chronic periprosthetic hip joint infection(II). Due to the low disease prevalence, registers would be a valuable sources for research data on chronic periprosthetic hip joint infection. We found an acceptable positive predictive value of the ICD-10 T84.5 discharge diagnosis code. We believe this code can be of use in future single-source register based studies, but preferably should be used in combination with alternate data sources to ensure higher validity.
We investigated the outcome of treatment following chronic periprosthetic hip joint infection in a non-selected population (III). We found a cumulative incidence of re-infection just below 15% in the follow-up period, regardless of treatment performed. We also found a high mortality rate, although causality cannot be established in the study. We also believe our study indicate bias in favor of two-stage revision, when compared to one-stage revision, as in study I, and that this aspect must be taken into consideration, when comparing different treatment procedures.

There is still much to be learned regarding chronic periprosthetic hip joint infections, and we believe, this thesis highlights important perspectives of treatment and outcome, to help initiate forward progression towards improved patient care.

Danish Summary

Kronisk infektioner i kunstige hofteled har altid været en frygtet komplikation. Disse infektioner er svære at behandle, og ødelægger potentielt alle de fremskridt som patienten har opnået ved behandlingen. På trods af 50 års forskning i disse infektioner, er vores mangel på viden på området stadig udtalt. Der er således et stadigt presserende behov for at forbedre denne viden. Formålet med denne afhandling var, at evaluere områder vedrørende behandlingen af kroniske infektioner i kunstige hofteled, med henblik på at optimere behandlingen.

Vi udførte en systematisk litteratur gennemgang(I), og undersøgte risikoen for af få en re-infektion efter behandling med en et-trins eller to-trins revision. To-trins revisionen bliver af mange betragtet som "guld standarden" i behandling af kronisk infektioner i kunstige hofteled. Ud fra vores analyser af tilgængelige literatur, fandt vi en marginal øget risiko for re-infektion efter en et-trins revision. Denne forskel var dog ikke klinisk relevant, og skal fortolkes i lyset af den lave kvalitet på de inkluderede studier samt den statistiske usikkerhed. Undersøgelsen understreger det store behov for forbedringer i de data vi har til rådighed, for at kunne afgøre hvilken behandling der er bedst.

Vi undersøgte om data fra Landspatientregistret kunne være til gavn i forskning i kroniske infektioner i kunstige hofteled(II). På grund af den relative lave forekomst af patienter med kroniske infektioner i kunstige hofteled i Danmark, ville dette register være en værdifuld kilder til forskningsdata. Vi fandt en acceptabel positiv prædiktiv værdi af diagnosekoden for infektioner i kunstige hofteled i dette register, og vi mener at det kan være til nytte i fremdig forskning.

Vi evaluerede resultatet af behandlingen af kroniske infektioner i kunstige hofteled i Danmark på udvalgte afdelinger(III). Vi fandt en risiko for at få en re-infektion lige under 15%, uanset hvilken behandling patient modtog. Dette er sammenligneligt med udlandske data. Vi fandt også en høj dødelighed hos disse patienter, selvom vi ikke kan fastslå, om der er en sammenhæng mellem at have en infektion og dødelighed, ud fra vores data. Vi mener desuden, at vores data indikerer, at tidligere undersøgelser indeholder systematiske fejlkilder til fordel for en to-trins revision, når sammenlignet med en et-trins revision, og at dette aspekt skal tages i betragtning, når man sammenligner forskellige behandlingsprocedurer.

Der er stadig meget, der kan forbedres ved kroniske infektioner i kunstige hofteled, og vi mener at denne afhandling, fremhæver vigtige perspektiver herved, som kan hjælpe den fremadretted udvikling imod forbedret patientpleje.

Background

"My dear Buchholz, nothing leaks out of stone..."
Sir John Charnley to his colleague Prof. H.W Bucholz

Revision Hip Joint Replacement

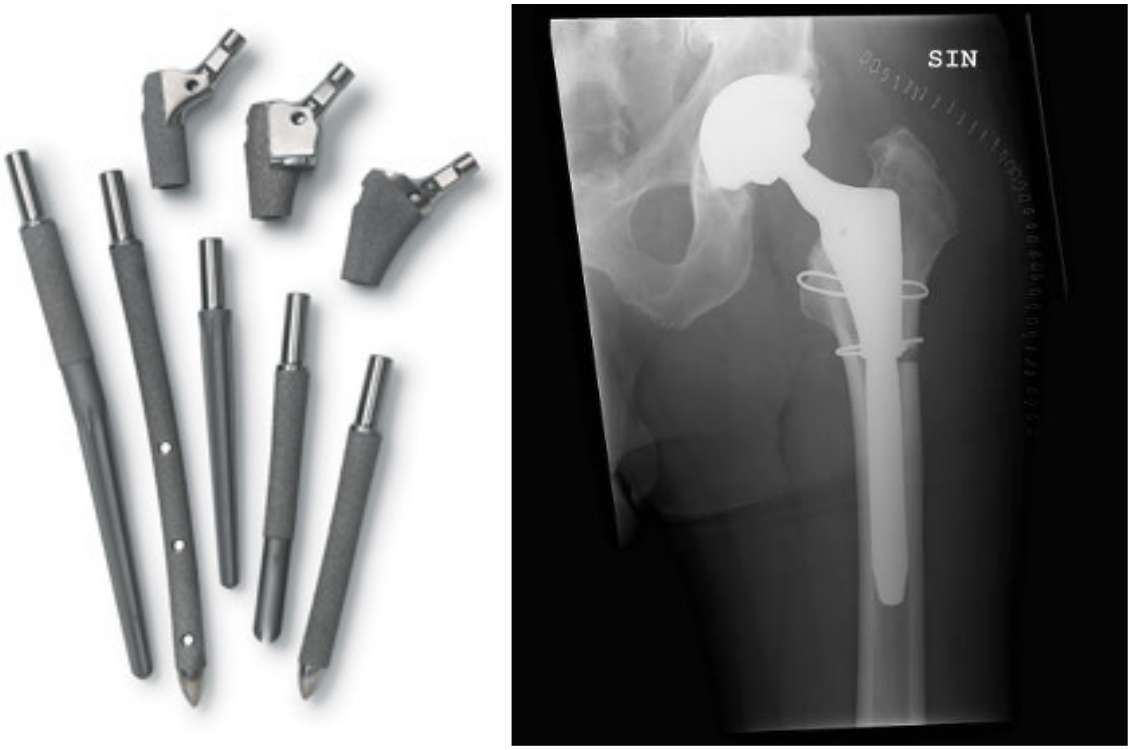
The value of hip joint replacement (HJR) is pronounced, and has since the evolution of the modern-day, low-friction, ball-and-socket hip arthroplasty by sir John Charnley[1] in the early 1960's, revolutionized the treatment of patients with severe disabilities, due to end-stage hip joint disease, being traumatic, degenerative, inflammatory, or infectious in cause.

However, as the absolute numbers of implanted primary HJR increased, so did the revision burden. In 2002, more than 43.000 HJR revisions were performed in the USA, and this increased to more than 50.000 revisions in 2006[2,3].

Revision surgery is far from the success of the primary procedure. Strong efforts are continuously made, to improve outcome following revision surgery. Mainly aiming at more secure implant-bone anchorage, and bone sparring procedures.
This is necessitated, as patients get younger when the primary HJR is performed[4], thus potentiate multiple revisions on the same individual during a life-time.
And also with higher physical activity level, with the revision HJR in situ.

In many years, revision procedures of total HJR were performed with bone cement (PMMA)[5]. But due to unacceptable revision rates in aseptic revisions, a shift took place towards a cementless technique[6].
Cementless revision is done predominantly with a modular femoral stem with distal femoral fixation, allowing the surgeon to adjust the axis of the femur more freely, and by-passing inadequate bone stock in the proximal femur[7,8](see picture 1).

Although limited evidence exist, for the value of a cementless revision compared to new generation cementing techniques[9-11], few surgeons today use a cemented technique in cases of poor proximal bone stock. And even with sufficient proximal bone stock, reserve cementation to low-demand individuals[9], or to cases with periprosthetic hip joint infections (hip PJI)[12].



Picture 1.
Left picture: A modular revision hip joint replacement with distal fixation, courtesy of Biomet©. Right picture: A conventional post-operative x-ray of a modular revision hip joint replacement with distal fixation. Cementless one-stage revision of a chronic periprosthetic hip joint infection performed by Prof. Kjeld Søballe.

The development of new techniques and implants, constantly aim to ease the burden of revision HJR, but one major concern still exist among orthopaedic surgeons, not hindered by these improvements: Infection.

Infection is today the 3rd leading cause of revision of primary HJR[13].
In the early days infection rates were high, but the work by Professor H.W. Buchholz and colleagues, set a benchmark for lowering infection rates following primary and revision procedures, by adding antibiotics to the PMMA[14-16].
This lead to a decrease in infections, which by the addition of adjuvant systemic antibiotic prophylaxis, has reach a seemingly low steady rate.
The value of the antibiotics in the PMMA is the reason, why advocates of cemented revisions still dominates the debate in chronic hip PJI[17], even though cementless aseptic revisions are preferred.

The Aspect of Biofilm

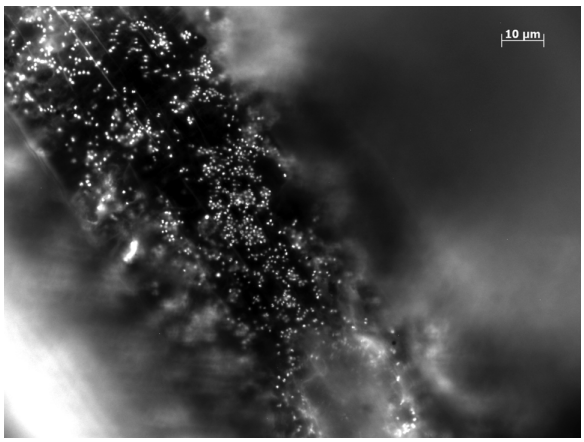
Biofilm in implant infections has come to the attention of the orthopaedic community in recent years[18,19] (see picture 2).
For many years, micro-organism causing periprosthetic joint infections in general, were believed to exist as planktonic organism. But in the last 3 decades, the importance of biofilm in implant infections has been introduced by Costerton and co-workers[20].
This has increased our understanding of treatment failures in all musculoskeletal and soft tissue infections.

Awareness to the level of surgical debridement, needed to clear these biofilm infections, and the necessity to remove *all* foreign objects during the revision procedure, to secure a successful outcome without re-infection, has evolved[21].

Micro-organism, living in a biofilm environment, is for all practical purposes resistant to all available antibiotics supplied systemically. Topical antibiotics diffusing from PMMA, is also no hinder for biofilm formation, even on the surface of the PMMA[22,23].

Micro-organism living in biofilm may also persist in a dormant phase, with altered internal metabolisms, making them difficult to culture by ordinary methods, and insusceptible to antibiotics aimed at disturbing the growth phase of the micro-organism[24].

Theoretically, these sessile, latent, chronic infections may persist for years, before external factors enables, or pushes, the colonization to a more virulent infection phase, such as in the case of a previously, well functional HJR, suddenly increasing in pain without apparent cause.



Picture 2.
Biofilm (the small shining dots) on a stainless steel pin (black background).
By epifluorescence microscopy.
Reproduced by kind permission of Nis Jørgensen[200]

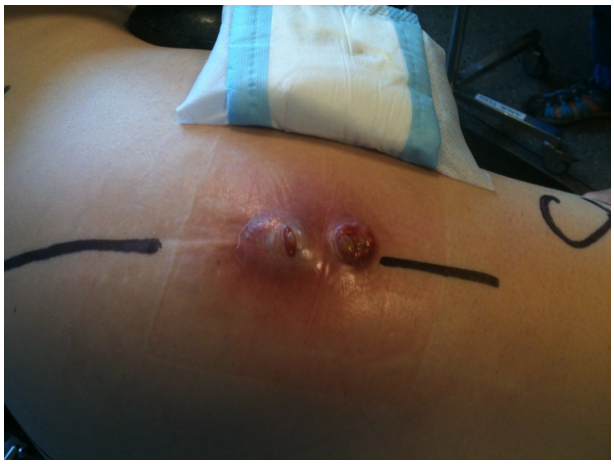
Biofilm has changed our perception of implant associated infections, and needs to be taken into consideration in all aspects of PJI, from diagnostics to treatment.

Periprosthetic Hip Joint Infection

Definition

How to define a hip PJI, and in essence re-infection, is surprisingly complicated.
But it is nonetheless of utmost importance.
Comparing patients with diabetes is easily done by a simple blood test. And outcome compared between treatments on blood sugar level, can easily be performed.
To compare outcome following treatment for chronic hip PJI, is more difficult, as we need to have a clear idea, of whether the patient samples are really uniform, which are probably rarely the case[25].

Two diagnostic parameters are thought to be pathognomic of hip PJI; a fistula to the joint (see picture 3) or a relevant sample of per-operative tissue biopsies with relevant growth in cultures (both described in detail below).

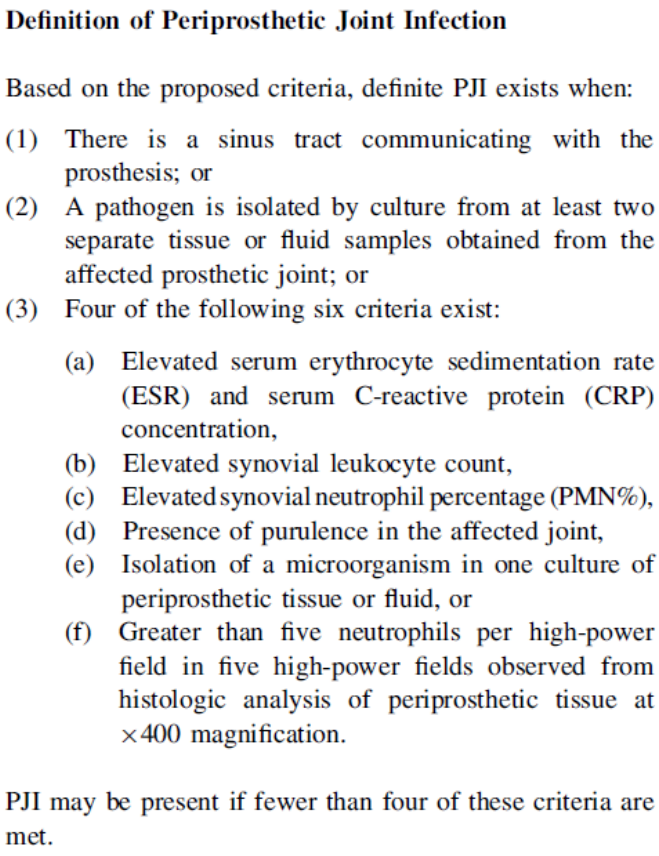


Picture 3.
Fistula to a hip joint replacement.
Patient at Aarhus University Hospital.

However, not all patients have fistula, and some may be culture negative[26].
Culture negative means, that no micro-organism is identified, even after acquisition of relevant samples, and clinical obvious signs of infection, e.g. existence of frank pus during surgery, or a fistula to the hip joint(III). This is often due to pre-operative antibiotic treatment, or inadequately processed samples[27].
Also growth of micro-organisms in cultures from joint aspiration or per-operative tissue biopsies, may be interpreted as contamination[28].

So hip PJI are a diagnostic elusive entity, and establishing, that an infection has not occurred, unless growth of a micro-organism or a fistula exist, is problematic[29,30].
Other findings may then have to be extrapolated by clinical inference, to determine the infection status of the patient. However, local availability of equipment and medical expertise, such as PCR techniques and nuclear imaging or histopathology done by dedicated pathologist, varies. As do local beliefs, in the diagnostic set-up making it very difficult to reach international consensus on the definition of hip PJI[30].

One recent, and often quoted, definition of hip PJI, is based on the work published in 2011 by the MSIS workgroup[29] (see Figure 1).



Definition of Periprosthetic Joint Infection

Based on the proposed criteria, definite PJI exists when:

(1) There is a sinus tract communicating with the prosthesis; or
(2) A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
(3) Four of the following six criteria exist:
   (a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration,
   (b) Elevated synovial leukocyte count,
   (c) Elevated synovial neutrophil percentage (PMN%),
   (d) Presence of purulence in the affected joint,
   (e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or
   (f) Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

PJI may be present if fewer than four of these criteria are met.

Figure 1.
The MSIS PJI definition. Parvizi et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin.Orthop.Relat Res. 2011;469:2992-4.

Although all studies in this thesis were initiated prior to 2011, the MSIS definition were for all clinical purposes, identical to that used in our studies.
We have based our categorical definitions of infection(II & III), on the premises laid out in our study protocols, combined with the MSIS definition.
Yet, our understanding of infection parameters continues to evolve, and with this our definitions[30,31].

Another important aspect in defining hip PJI is time.
Has the patient a chronic infection, or is it an acute hematogenous infection.
And when do we go from acute/early infection to a delayed/late/chronic infection.
Numerous definitions, and synonymous, are used to define these time frames, and are based on both the time since latest surgery to the joint, and/or the duration of symptoms.
The problem is further, that these time frames are used interchangeably, both in comparison between groups for research purposes, or for dictating the choice of treatment[19,32]. Which may interfere with a direct comparison between groups[25].
Time since latest surgery can be established with ease, but recall bias unquestionably exist, when patients needs to account for duration of symptoms.
Also, what may be a relevant symptom for the physician, may be neglected, or interpreted differently by the patient.

The clinical relevancy of determine the time frame of the infection, is not to be discarded, giving our novel insight into biofilm. As biofilm formation occurs within hours of colonization, and micro-organism may stay dormant for years, before being activated, the boundaries for when to perform exchange procedures, must necessarily change accordingly.

Epidemiology

As noted previously, hip PJI is the 3rd leading cause of revision, with almost 8.000 registered revisions performed in the USA in 2006[13]; in absolute numbers, the same as primary HJR implanted annually in Denmark[33].

Yet, the true incidence of hip PJI will probably never be established. There are several reasons for this.

An unknown number of patients are never registered in administrative databases, were large-sample incidence is established. This due to death before surgical intervention, patients maintained on suppressive antibiotic treatment, or patients erroneously classified in the registers. Patients may also be clinically interpreted as aseptic loosening, when in fact the patient has a low-grade chronic hip PJI.

The cumulative incidence of hip PJI has for long believed to be around ½%. This number is often reported in published literature, without a time reference, and without discriminating between primary or revision replacements.

A recent large-sample register study has indicated, that the "minimal" 5-year incidence is 1.03%(95%CI 0.87-1.22) following primary HJR in Denmark. Which is our best, most "true" estimate to date[34].

Others have found this to be even higher, with a 2-year and 10-year cumulative incidence of 1.63% (95%CI 1.5-1.8) and 2.2% (95%CI 2.1-2.3) respectively in the Medicare population in the USA (the 95% CI is estimated via data obtained in the article, as this is not stated in the original paper) [35].

The authors of the Medicare population paper did note, that when elective HJR were considered separately, the cumulative incidence decreased by 50%, which could explain the higher cumulative incidence as compared to single-centre/surgeon series.

Incidence of hip PJI, after aseptic revisions, has not been thoroughly evaluated, and information on this is very limited. The cumulative incidence is nevertheless, believed to be substantially higher, than following primary procedure[36].

A 90-days post-operative cumulative incidence of approximately 3% has been reported. Wolf et al reported 2.9% (95%CI 2.8-3.0) in the Medicare population (95%CI is estimated via data obtained in the article, as this is not stated in the original paper) and Lindberg-Larsen et al reported 3.0% (95%CI 2.3-4.0) in a Danish cohort[6,37].

But long-term, large-sample, follow-up data are not available to our knowledge.

Patients with hip PJI are costly for society. Projections indicate, that we may face a genuine rise in incidence of hip PJI[38,39], which will further increase the burden on our health care systems. Estimation of the societal cost, projects that 1 billion USD will be spent in 2014, in the USA alone, treating periprosthetic hip and knee joint infections. With an average total charge of treatment, per infected hip joint replacement, exceeding 90.000 USD in the USA, as of 2009.

Updated estimations do not indicate, that the economic downturn in the last 1½ decade, has altered these previous projections[40].

Identification of risk factors for developing hip PJI, are essential in the effort to decrease the number of infections, by increased awareness, and potential avoidance or optimization of these[41].
Many aspects has been proposed as risk factors[42,43], but only very few thoroughly investigated and classified. Antibiotic prophylaxis can be regarded as one with solid evidence for[44].
Again, the relatively few patients, and the wide demographic diversity, encountered in single-centre studies, makes it difficult to perform such evaluations locally[41].
And many of the theoretical potential risk factors, are not registered in administrative or clinical registers.
There is an overwhelming amount of suggested potential risk factors. To name just a few, recent studies have identified a higher CCS[41], depression[45], obesity[45-47], cardiac arrhythmia[45], male gender[45,48], longer surgical duration[41,48], substance abuse[49], chronic liver disease[49,50], previous surgery[50], chronic corticoid therapy[50], rheumatoid arthritis[46,51], coagulopathy[46], pre-operative anaemia[46], higher ASA-score[41], and low hospital and surgeon volume[41] as risk factors of developing hip PJI following primary HJR.
However, many of the studies are mutually exclusive, meaning that they do not indentify risk factors determined in other studies. Also causation and/or effect modification are rarely discussed.
In summary, we lack useful clinical information on important risk factors, which would enable us to take measures against these, and thereby optimizing the chance of avoiding infection[42].

Diagnosis
One can divide the diagnostic criteria to pre-operative and per/post-operative.
The pre-operative diagnostic criteria consist of examinations, meant to give an accurate idea, of whether a hip PJI is really what complicates the patients HJR.

Pathognomic value is usually attributed to the presence of a fistula.
A fistula, in this regard, is the presence of a soft tissue-covered passage, from the outer skin to the joint space (see picture 3).
As the joint is now susceptible to the entry of micro-organisms, the cause of the fistula is indifferent, as the joint space is doubtlessly colonized.
However, even though a general consensus of this exist in the orthopaedic community, the true pathognomic nature of a fistula regarding hip PJI is scarcely investigated[42]

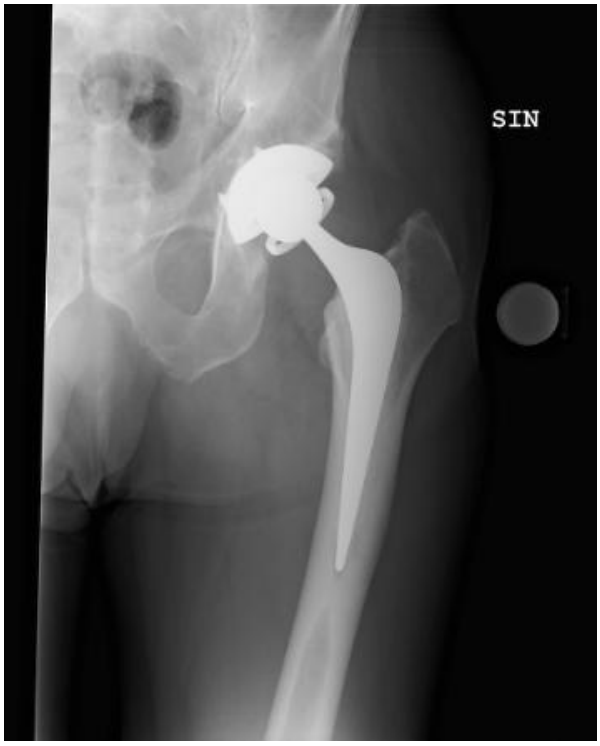
Serological blood markers are the oldest, and most adapted classification criteria [52]. But, these must be seen as surrogate markers of infection, depending on a humane immune response, and as such, not directly related to a hip PJI.
The most applied, and recommended, serological markers are C-Reactive Protein and Erythrocyte Sedimentation Rate.
These can, however, be elevated due to a number of diseases, not related to an infection in a HJR. Nevertheless, the negative predictive value of these two markers, has been found

consistently high[53,54]. And according to the latest published guidelines from the American Academy of Orthopaedic Surgeons, remain very useful as a screening tool[42].
White blood-cell count fail in general in evaluating hip PJI[52,53].
Serum interleukin-6 is a promising, acute fase-reactant, emerging in the past decade. Similar to C-Reactive Protein, but with a profile, which seems better suited for hip PJI[53,55-57]. This marker has, not yet gained widespread applicability in the orthopaedic community in Denmark. An array of other serological markers are in the pipeline[58,59], but all facing the same scientific problem. The lack of an accurate diagnostic "gold-standard", to which to compare.

Pre-operative joint aspiration is a longstanding, commonly applied method, of distinguishing aseptic from septic complications[60]. In some centres, this is repeatedly done, until positive cultures is acquired, before proceeding to surgical intervention[17,60].
To improve the diagnostic value of joint aspiration, evaluation of white blood-cell count, or PCR detection of micro-organism genomics, has emerged in recent years. The first showing promising result[61,62], the latter not[63].
And last year, the preliminary results of a simple urine strip test for leukocyte esterase and glucose were presented, which further could improve the evaluation of joint aspiration[64,65].
Consensus is nevertheless[42], that hip joint aspiration should only be performed in patients with a high suspicion of infection, due to technical aspects, such as dry taps and processing of the aspirate. Dry taps means, that no fluid can be aspirated from the joint, which are frequently encountered in the hip joint. This do not indicate, that an infection is not present, merely that no material can be recovered from the joint for examination.
And if a "wash-out" is attempted, with installation of sterile saline water, the biochemical evaluation cannot be performed. Also, an introduction of micro-organism into the joint, during the aspiration procedure, or false-positive results, are concerns, that must be taken into consideration.

Conventional x-ray is neither specific nor sensitive for periprosthetic hip joint infection. In case of observed pathologies on x-ray, one is sure, that something is wrong, but the cause of this remain unknown, and can rarely be discriminated as being septic or aseptic.
If nothing is pathological, an infection may still be present, as bone reactions, visible on x-ray, takes time to develop[66,67] (see picture 4).
However, the role of conventional x-ray in pre-operative planning is vital, and other causes to the hip symptoms, may be evaluated. As such, conventional x-ray remain a first-line exam in evaluating the symptomatic HJR.

Picture 4.
Conventional x-ray of a chronic periprosthetic hip joint infection. No pathological changes are visible. Pre-operative x-ray of patient in picture 1.



Magnetic Resonance Imaging (MRI) are generally suited to evaluate soft tissue complications, such as infections. But metallic artefacts generated by the HJR is still a problem[68]. Although recent advances in MRI scanning protocols may have improved the quality of the imaging obtained[69],no evidence exist, regarding the value of MRI as a specific diagnostic tool in periprosthetic joint infection[42,70].
Computed Tomography (CT) scan gives a spatial resolution, not obtained in ordinary x-ray, and may be able to identify changes to the bone better, than conventional x-ray. But CT also lacks the ability to differentiate on the cause of the observed changes, and metallic artefacts are also an issue[71]. Changes brought on by infection has also been limited investigated by CT[72].
Due to this, MRI and CT are very infrequently reported in studies on hip PJI, and are not currently recommended as first-line procedures[42]

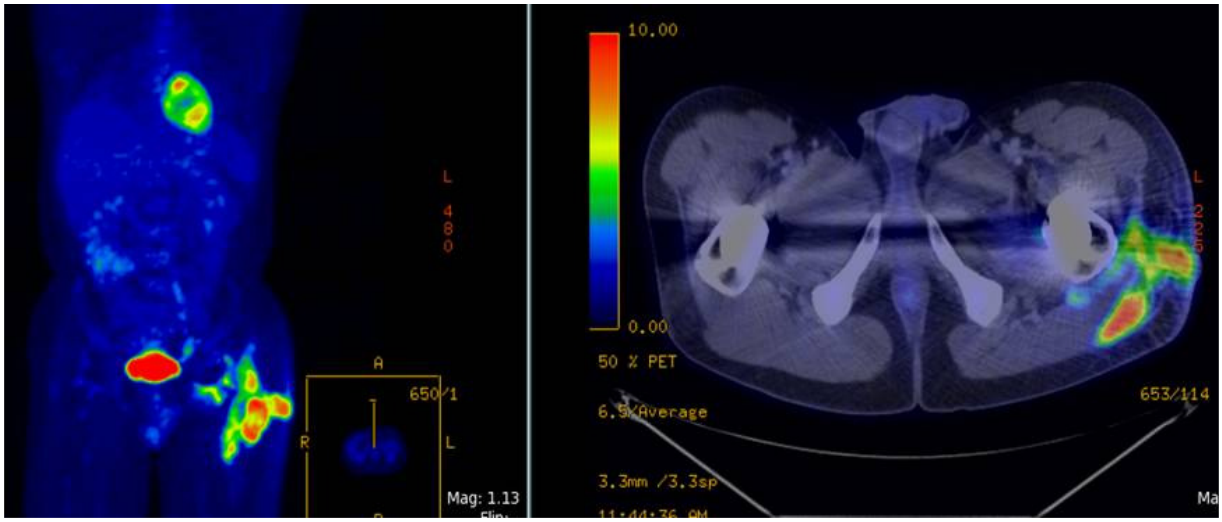
Nuclear medicine imaging is also a longstanding tool in diagnosing hip PJI[66,73,74].
The available methods are somewhat hindered by the labour-intensive requirements, invasiveness of the exams, availability of the scanners, cost, and the medical expertise to interpret the scans.
The key aspect of all nuclear imaging modalities, are the injection of a tracer into the patient, which targets different processes in the body.
These are areas of metabolism, e.g. in Positron Emission Tomography (PET) scan; bone turnover, e.g. in bone scan; chemotaxis by active infection, e.g. in white blood-cell scintigraphy.

All of which are believed to be present in periprosthetic joint infection.
Nuclear imaging depicts planar images, but the recent advances in Single Photon Emission Computed Tomography /CT[75] and PET/CT has helped obtain combined 3-dimensioinal images (see picture 5A+B).
This 3-dimensional image potentially allows the surgeon, to pre-operatively identify hot spots for tissue sampling, and determine focus of aggressive debridement during the revision procedure. Although the value needs to be established.
Unfortunately, the result presented by planar nuclear medicine imaging have a large spread in sensitivity and specificity[66,73,74].
Several reasons for this exist per protocol, but especially the existence of biofilm in PJI could attribute.
To our knowledge, tracers are under development, that targets surface molecules of biofilm. This could potentially revolutionize the nuclear imaging pre-operative diagnostics, but are far from being applicable to clinical use.

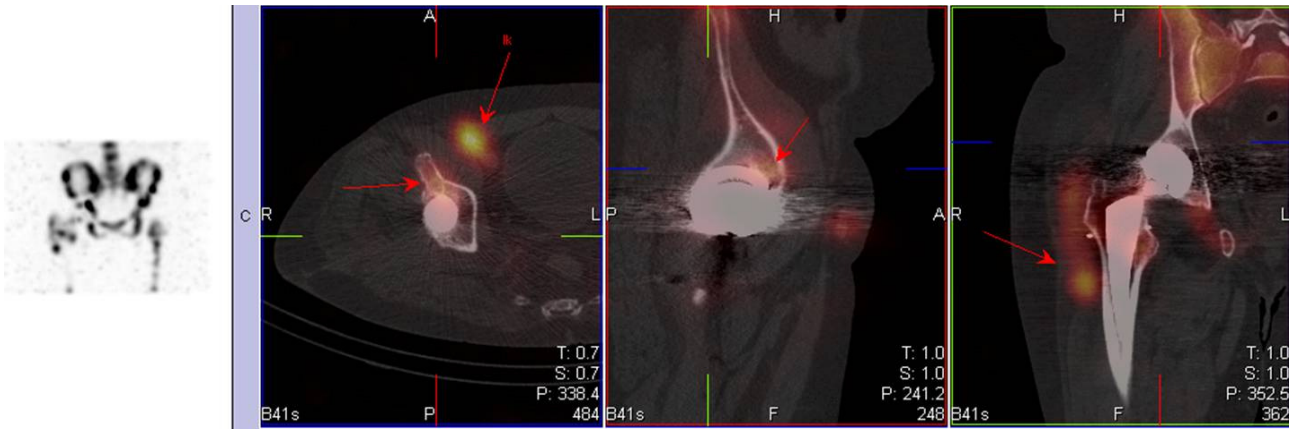
Per-operative tissue biopsies is considered to be the pathognomic "gold-standard", to which other modalities are frequently compared. Yet, the sensitivity and negative predictive value of these remain low(III), which will impair the comparison to other diagnostic modalities.
The techniques of tissue sampling, and the laboratory processing of these samples, are not uniform worldwide[27]. The technique of sample acquisition has in Scandinavia been guided by the work published by Kamme and Lindberg in 1981[28,76]. This is not a widely used international approach, and in many centres, no uniform acquisition of samples apparently exist[42]. The location of acquisition of samples, and the number of samples, are very often not systematically performed, as it is, at the discretion of the surgeon, on how to handle this matter[27,77]. After the acquisition of samples, recent studies indicate, that the often used incubation period of 3-5 days is insufficient, and that we need to institute prolonged growth[78,79].

Per-operative histopathology is highly regarded amongst the centres with the availability of this examination[42]. It is one of the key criteria in the MSIS classification[29], but it is not a pre-operative test. Also, it is impaired on sensitivity in case of low-grade infections[80].
A discussion of the interpretation of samples are currently debated, as to optimize the validity of the method[81]. In Denmark, there is a lack of trained pathologist, and per-operative histopathology is seldom performed. But if an experienced pathologist, capable of performing adequate sample processing and evaluation is available, the method appears very strong in predicting the presence of infection[82]

Many other diagnostic modalities are emerging in these years, especially based on the knowledge of biofilm.
Sonication of implants to extract bacterial matter, which can then be cultured, is one of the more interesting and investigated methods[83]. But the introduction into clinical practice remain.



Picture 5A.
PET/CT of a periprosthetic hip joint infection.
Left picture: Planar PET-scan.
Right picture: Combined 3-dimensional image.



Picture 5B.
Dual-Isotope Bone marrow/Leukocyte Scintigraphy Single Photon Emission Computed Tomography /CT of a periprosthetic hip joint Infection.
Far left picture: Planar scintigraphy
3 right pictures: Combined 3-dimensional images.
Reproduced with kind permission of Ramune Aleksyniene, Department of Nuclear Medicine, Aalborg University Hospital.

Molecular biology is another emerging modality, with PCR being the cornerstone of identification of gene material from implant-colonizing micro-organism[84,85], however lack of antibiogram and false-positive results are concerns.

All things aside, the orthopaedic community still faces great endurances in establishing uniform, and evidence-based criteria, for hip PJI, which is needed to accurately evaluate risk factors, treatment and prognosis.

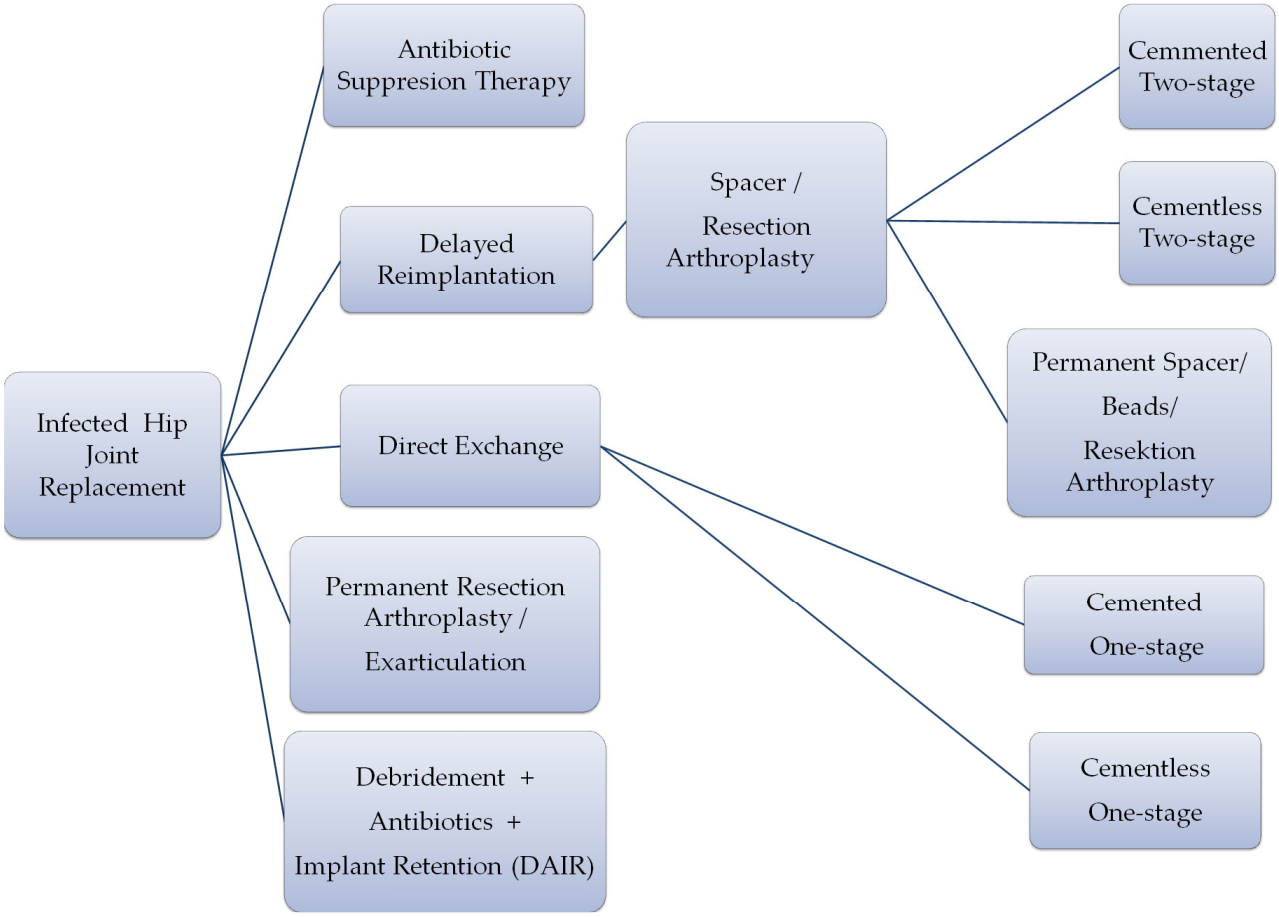


Figure 1. Potential treatment scenarios of chronic periprosthetic hip joint infections.

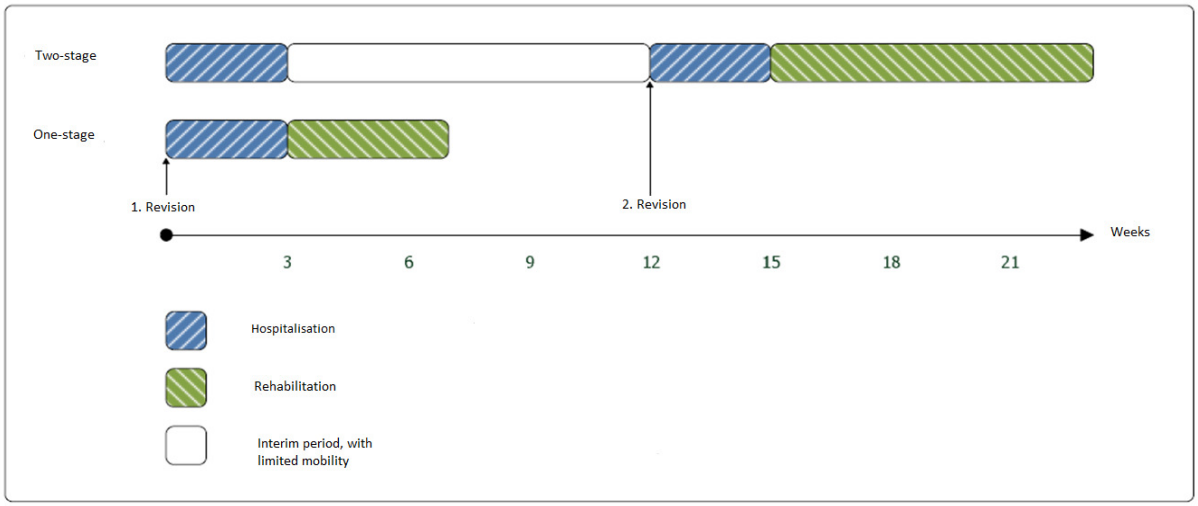


Figure 2.
Illustration of the differences between a one-stage and two-stage revision strategy.

Treatment Options
The only curative treatment option of chronic hip PJI is surgery[86].

In some cases, patient do not wish further surgery, and can accept the symptoms endured from a chronic hip PJI, while the infection is being suppressed with life-long antibiotic treatment.
In a few cases, surgery is not an option, due to an eminent risk of death, also here life-long antibiotic treatment may play a role[19].
In all other cases revision surgery is the only option, as curative treatment of peri-implant infections, purely with antibiotics, is by all experts opinion destined to fail[19,86,87].

Revision surgery can be performed in many ways and with several objectives in mind (see figure 1).
In cases of patients with subsequent limited mobility, a permanent resection arthroplasty can be the preferred treatment of choice.
This method is also used in countries, with limited access to health care systems, and do show acceptable results, with no pain and fair mobility[88]
In very rare cases, a hip exarticulation may be a life-saving procedure.
Debridement, antibiotic treatment and implant retention (housecleaning) is not a first-line option for chronic hip PJI[89]. It is primarily reserved for cases of post-operative or acute hematogenous infections[19,90]. But in cases of fragile patients, where a re-implantation procedure is not feasible, this is a potential treatment option, to minimize the infection burden, and aid the following antibiotic suppressive treatment[91].
The ultimate goal of revision surgery for chronic hip PJI is a patient with a functional prosthesis in situ and with cleared infection.
This can be achieved by a delayed re-implantation procedure or via a direct exchange (see figure2).
Delayed re-implantation is often performed, as a two-stage revision procedure, in which the infected implant is removed, an interim period of weeks to months follows, after which a new HJR is implanted[92-96].
This re-implantation was in early years done with PMMA, but in recent years, cementless re-implantation in the second stage, has been more commonly performed, without a negative effect on clinical outcome[25].
In the interim period (the white area in figure 2), the patient is left with limited mobility of the hip joint.
Although often named two-stage revision in literature, multiple debridement may be performed in the interim period, adding to the value of this procedure.
On the down side, these extra debridement, demands additional anesthetic procedures, and potentially introducing new micro-organism to the joint during surgery.
Two-stage revision is currently accepted as the "gold-standard" in treatment of chronic hip PJI[19,97].
Direct exchange is performed as a one-stage revision, in which the infected HJR is removed, a thorough debridement performed, and immediately implantation of a new HJR (see figure 2).

Carlsson and colleagues from Lund University published in 1978, the first rigorous description of cemented one-stage revision, with appropriate application of systemic antibiotics post-operative[98]. Shortly followed results, published by Buchholz and colleagues in 1981[99].
One-stage revision has mainly been practiced in European countries[17]. However, renewed international interest for a one-stage procedure is currently flourishing, as result of this method continues to yield comparable results to delayed re-implantation[17,25].

The focus on PMMA, delivering topical antibiotics, has been a paramount issue, in one-stage revision surgery, originating from the work of Prof. Buchholz[12]. This is the single most important cause, why cementless one-stage revision historically has not been performed, as has been the case in aseptic revisions.

In 2009, Winkler and colleagues published the first results on cementless one-stage revision on 37 patients[100].
These were a mixture of acute and chronic infections, but results were promising.
A strong belief on the quality of debridement, and the effect of the antibiotics in the allograft used during the revision procedure, lead him to believe, that this was a plausible method (personal communication with Dr. Winkler, Copenhagen 2014).
This was in accordance with the belief of Prof. Søballe based on observations following suspected aseptic revision, where the intra-operative samples grew micro-organism. These "one-stage" revisions still maintained an apparent low re-infection rate[101]. We therefore initiated a clinical, prospective, longitudinal, multi-center, proof-of-concept study in 2009, investigating the value of cementless one-stage revision (www.clinicaltrials.gov NCT01015365), which awaits finalizing of follow-up in 2016.
The value of a cementless revision compared to a cemented in hip PJI, is believed equivalent to those for aseptic revisions.
Since the initiation of our clinical study, a few studies have been published on this method, yet the total amount of cases remain limited[25,102].

Whether to perform a one-stage or two-stage revision is continuously debated, and consensus is not agreed upon[17,25,97,103-107].
One vital aspect of treatment, is to select the right patient for the right procedure, but as high-quality comparative studies are non-existing, this is still based on local cultures and beliefs.

Outcome of Treatment

Current literature has focused on whether or not the patients remain clinically free of infection following surgical intervention.

In the earliest reports[98,99], clinical success, defined as patients remaining free of infection, was reported below 80%. This has increased since then.

Today it is believed, that treatment cures 9 of 10 hip PJI, regardless of whether a one-stage or two-stage revision is undertaken[25,106,108].

Nevertheless, the risk of infection is still 3-10 fold that of aseptic revisions and primary procedures, and the clinical success must be seen in light of merely including re-infection as outcome.

Recent reports also indicate, that patients with a chronic hip PJI, may actually have an increased mortality[109-111].Furthermore, aseptic revisions are seldom individually highlighted.

How the patient actually perceives the treatment, have been investigated on a miniscule level. Quality-of-life assessments, are primarily investigated as secondary to clinical outcomes[94,112]. And in essence, no stringent evaluation of patient assessment of quality-of-life following treatment of chronic hip PJI actually exist to date.

Aim of Thesis

The overall aim of this thesis was to investigate epidemiological and clinical aspects of chronic periprosthetic hip joint infections, in particular concerning treatment and outcome.

I
The aim of this study was to compare two-stage revision to one-stage revision in treatment of chronic periprosthetic hip joint infection in present published literature.

II
The aim of this study was to establish the positive predictive value of the T84.5 ICD-10 discharge diagnosis code, relating to periprosthetic hip joint infection, in the Danish National Patient Register.

III
The aim of this study was to evaluate the prognosis of chronic periprosthetic hip joint infection in a multi-centre, non-selected, population with focus on re-infection in the presence of competing events.

Materials & Methods

Study Designs

Study I was performed as a systematic review of previously published literature on one-stage and two-stage revision following chronic periprosthetic hip joint infection with coherent meta-analysis of available data.

Study II was performed as a cross-sectional study of ICD-10 discharge diagnosis codes for patients registered in the Danish National Patient Register following surgical treatment for periprosthetic hip joint infection.

Study III was performed as a longitudinal follow-up study by establishment of a retrospective cohort of patients registered in the Danish National Patient Register following surgical treatment for chronic periprosthetic hip joint infection.

Study I was reported in accordance with the *Proposed Reporting Items for Systematic reviews and Meta-Analysis*[113,114], and II & III in accordance with the *Strengthening the reporting of observational studies in epidemiology* statement[115].

Sources of Data Acquisition

The Online Article Databases

Identifying, and retrieving, health sciences literature has been revolutionized by the forthcoming of online article databases. Among the most used, in search of medical literature, are the two major databases: Medline/Pubmed Central® and Embase®.
These online article databases enable researchers to obtain relevant published literature, fast and reliably.
Search strategies can be applied to the different databases, either as hierarchically structured searches, or as words of free texts, and has been found robust[116]. Yet, a rigorous search strategy must be planned, to optimize retrieval of relevant material[117,118].
We used such online article databases to retrieve relevant literature on the matter of chronic hip PJI (I).

Pubmed Central® is maintained by the United States National Institutes of Health's National Library of Medicine, and is open access.
Initiated in 2000, the archive now includes 3.3 mio. articles, provided by 1637 fully participating journals, and other collaborators, with material dating back more than a century in some cases (http://www.ncbi.nlm.nih.gov/pmc).

Embase® is maintained by Elsevier®, and is user paid.
This archive contains more than 28 mio. indexed records from over 8.400 journals, dating back to 1947 (http://www.elsevier.com/online-tools/embase).
Free access is provided to researchers associated to the State University Library, Aarhus.

We also applied the search strategy to The Cochrane library (http://www.cochranelibrary.com), for the identification of appropriate reviews, and the World Health Organization's platform of international clinical trials registry (http://www.who.int/ictrp/en), to allow identification of currently active, or previous performed, registered clinical trials.

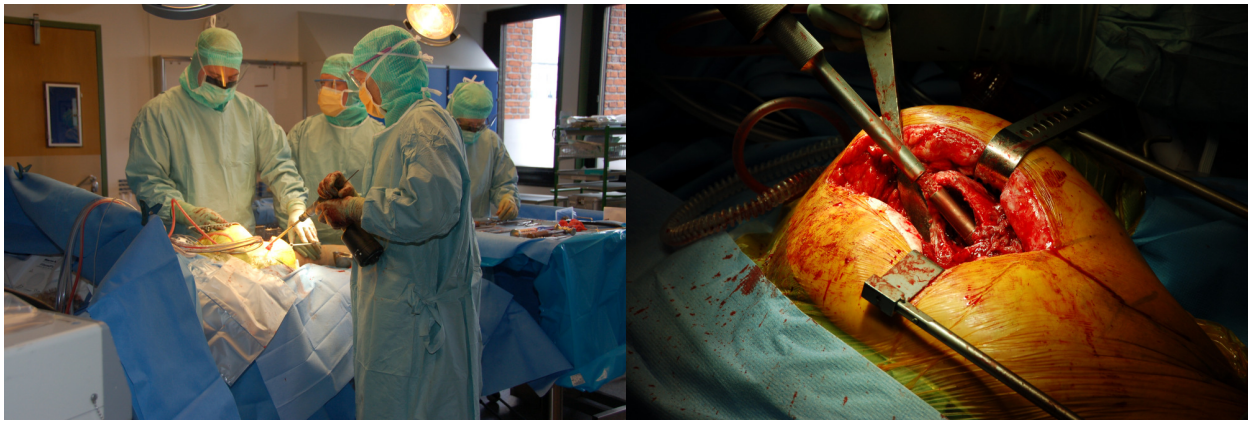
The National Administrative Register

The Danish National Patient Register (DNPR), currently located under the administration of "*Statens Serum Institut*" (http://www.ssi.dk/English), enables researchers to acquire information on inpatient and outpatient treatments, performed at both public and private hospitals in Denmark[119].
Initiated in 1977 for administrative purposes, it has as such been used since, including application for financing purposes of hospital activities.
Due to the integrative network with other public administrative databases, the use in epidemiological research has expanded. The Danish population, in this sense, pertains to a nested cohort[120], with information on birth, death, and other demographic, and medical aspects, incorporated in the integrated database network.
Data in the DNPR are collected on a electronically day-to-day basis, and can be linked to other network databases, via the nationally adapted, unique, lifelong CPR number.

The CPR number is assigned to all registered Danish citizens at birth, or when granted citizenship [120,121]. The register contains information on inpatient contacts since 1977, and emergency room and outpatient contacts since 1995. Private hospitals has been included since 2002.
Registration to the DNPR is generally believed to be with high completeness, although dark numbers may exist, in light of the emerging private hospital sector and insurance financed treatments performed[119].
The ICD-10 discharge diagnosis codes has been applied since 1994, and the NCSP has been applied since 1996[119] .
Extraction from the DNPR is performed by the *Statens Serum Institut*, based on a priori defined variables supplied by the researcher upon requisition of data.

The Departments of Orthopaedic Surgery
The health care system in Denmark is based on a free, and equal, access to health care services at public hospitals, who to-date still delivers the vast majority of health care services provided in Denmark.
The health care system is financed by income tax revenues, which renders a non-financial relationship, between the treating physician and the patient.
In principal, the Danish orthopaedic surgeon has no personal gain by performing one procedure over another.
As such, revision of a failed HJR are accessible on equal terms to all Danish citizen, and the treatment initiative are not based on the financial aptitude, but on a full consideration of the potential gain of the procedure, patient and surgeon conjoined.

In Denmark, all total HJR revisions are performed by orthopaedic surgeons, specialized in adult reconstructive surgery (see picture 6).
In the case of revision surgery for hip PJI, an individual treatment strategy is decided at the discretion of the treating orthopaedic surgeon, in close collaboration with the patient (see figure 1). A two-stage revision strategy being the national standard of care.



Picture 6.
Revision hip joint replacement performed at Aarhus University Hospital, Denmark.

The departments of orthopaedic surgery, involved in studies II & III, was recruited within an existing research collaborative[122]. The involved departments performed just under one-third of all primary HJR, and more than one-third of all revision HJR procedures in Denmark in 2008-2009. The departments were believed to contain a relevant case-mix distribution to ensure national and international comparability[33].

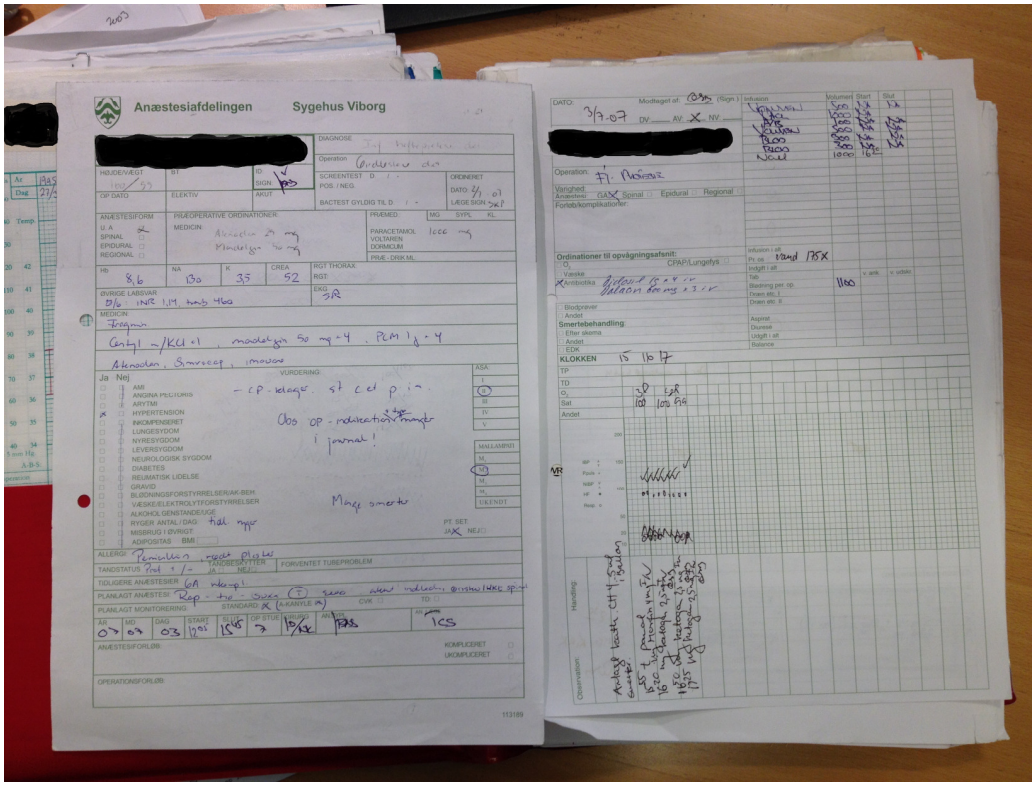
The Medical Records

Medical records in Denmark has two forms: Paper and Electronic. In the past two decades, the emerging of electronic patient medical records, has taken place in all public hospitals in Denmark.

However, this has not been done in a coordinated effort, and many different systems are in use, few enabling true interaction.

Due to this, a manual medical record search was conducted (II+III), in both paper and electronic patient records of the individual hospital.

Much of the information sought existed merely in paper charts, such as information from the anesthesiologist charts (see picture 7), and relevant data was extracted from these.



Picture 7.
Paper chart containing information concerning the anesthesia during revision procedure including ASA score and blood loss.

Aspects Relating to Study Populations

We initially adapted the McPherson staging system[123] to the studies in this thesis, and agreed that symptoms over 4 weeks of duration *and* time since latest surgery over 6 weeks, did indeed denote chronic nature.
However, the limits remained fluid, and in gray-zone patients, depended on a case-by-case evaluation of the available information.
Especially when data was of retrospective nature, and the information did not allow such stringent limits of definition.

Study I
We believed the issue of re-infection, after a performed re-implantation following revision for a chronic hip PJI, to be the feasible relevant clinical aspect to investigate.
For patients to be included in the meta-analysis, a diagnosed chronic infection of a HJR, treated with re-implantation in either a one-stage or two-stage revision, and information on re-infection, had to be available.
We applied a novel search strategy to the before mentioned online article databases. In extension to the acquired articles, snowballing was performed. Snowballing is the process, in which a review of the reference list of the acquired articles is done, and extending the search strategy to these as well.
We finally evaluated 165 full-length articles, of which 36 studies[32,93,95,124-156] were included in the review, and data extracted for the meta-analysis (see figure 4).
None of the included studies directly compared one-stage revision to two-stage revision.
The vast majority (92 %), of the included studies could be defined as case-series pertaining to description of results, following either a one-stage revision or a two-stage revision.
Three-of-four studies were retrospective of nature. The overall methodological quality of the included studies, in light of the aim of the systematic review, were low.
Due to the methodological nature of the available literature, we adapted a pragmatic approach, and defined *periprosthetic hip joint infection* in an article-to-article evaluation, using a palette of definitions, including such simple statements, as by the authors of the article proclaiming the patient had a chronic hip PJI. Data was extracted as available in the published articles, and no effort was made to obtain the original data from the authors.

Study II
We extracted data from the DNPR, including CPR number, on patients registered with an ICD-10 discharge diagnosis code of T84.5, *Infection and inflammatory reaction due to internal joint prosthesis*[157].
T84.5 is the sole discharge diagnosis code relating to periprosthetic joint infection, but is site independent.
As we were only interested in hip joint affections, the search was specified, by using NCSP procedure codes relating to hip joint affections, in this case hip joint infections and/ or an existing hip joint replacement (see figure 5).

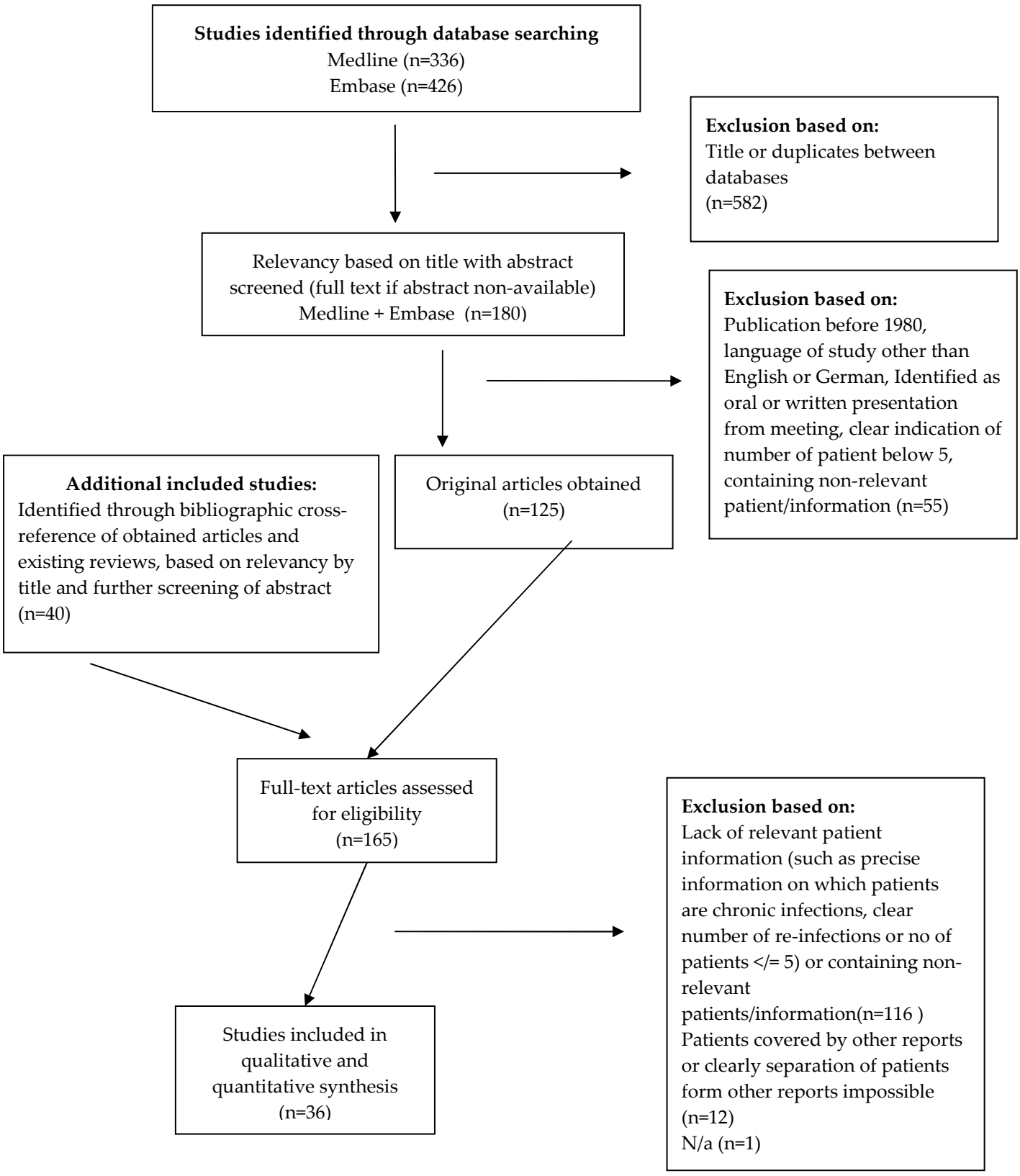


Figure 4.
Flow-chart for inclusion in study I

KNF Cxx:	Secondary prosthetic replacement of hip joint
KNF G09:	Excision arthroplasty of hip joint
KNF G19:	Interposition arthroplasty of hip joint
KNF G29:	Other arthroplasty of hip joint without prosthetic replacement
KNF S19:	Incision and debridement of infection of hip joint
KNF S49:	Incision and debridement of infection of hip joint with introduction of therapeutic agent
KNF U0x:	Removal of a partial prosthesis from hip joint
KNF U1x:	Removal of a total prosthesis from hip joint
KNF U89:	Removal of therapeutic implant in treatment of infection of hip or femur
KNF W69:	Reoperation for deep infection in surgery of hip of thigh

Description:
The first three letters describe placement in the procedural hierarchy in descending order. K denotes *classification of surgery*; N denotes *musculoskeletal procedures;* F denotes *procedures on hip and femur;* x in the number denotes that more numbers may be applied to that position, e.g. KNFC20 is a cementless total hip arthroplasty and KNFC40 is a cemented total hip arthroplasty. In this case, all available combination has been applied in the search.

KNFS 19, KNFS49, KNFU89 and KNFW69 are infection-specific codes. The remaining codes are noninfection-specific. Infection-specific do not pertain exclusively to prosthesis infections, but can also be used for instance in native joint infection.

Figure 5.
NCSP procedure codes used to restrict the search to the hip joint

For logistic reasons, we defined a time frame of 6 years, to be an appropriate interval, to investigate the positive predictive value of the ICD-10 code.
Furthermore, to ensure an adequate follow-up time, and a modern cohort in study III, this period was set to 2003 - 2008.
We identified 283 patients with an ICD-10 discharge diagnosis code of T84.5 (see figure 6). We investigated only the first registration with an T84.5 code, in the defined time frame, for each patient.
It is noteworthy, that of the 283 patients, 6 (2%) had infected osteosynthesis implants, and were clearly misclassified, as they should have been coded with T84.6, *Infection and inflammatory reaction due to internal fixation device [any site]*[157].

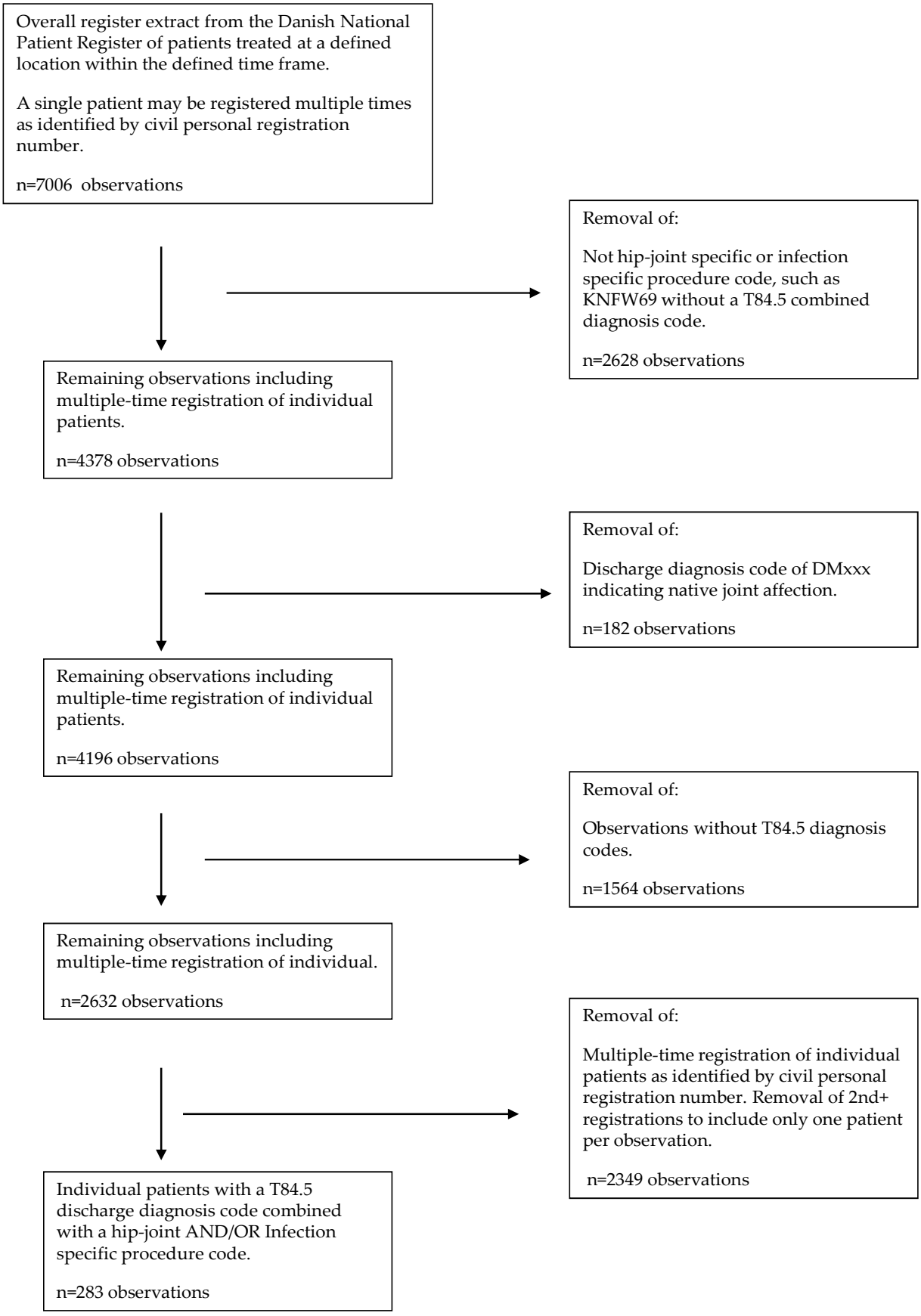


Figure 6.
Flow-chart for inclusion to study II.

Study III

In combination with the search strategy in study II, extraction of data from the DNPR in patients registered with a NCSP procedure code relating to an infected hip joint replacement and independent of ICD-10 code was also performed (se figure 5).
This was done to identify a cohort of patients, surgically treated for a chronic infected hip joint replacement between 2003 to 2008.
By the combined search strategy, 461 CPR numbers were extracted. A manual review of the medical records of these 461 patients, left 130 patients verified with a treatment procedure performed for chronic hip PJI in the defined time period (see figure 7).

The DNPR can furthermore be used to estimate the CCS score[158,159], and we extracted information on the included patients registered co-morbid conditions, 5 years prior to their index revision procedure.
A thorough medical record review was performed for each patient, with extraction of numerous clinical, and paraclinical, data relating to patient demographics, and treatment, of the chronic hip PJI.
We were able to perform follow-up via the nationwide electronic patient records "e-journal" (http://www.regioner.dk/sundhed/sundheds-it/e-journal; In Danish only). This enabled us, to obtain information on vital status and treatments done to the hip in question nationwide, and not just for the individual department, in the entire follow-up period.

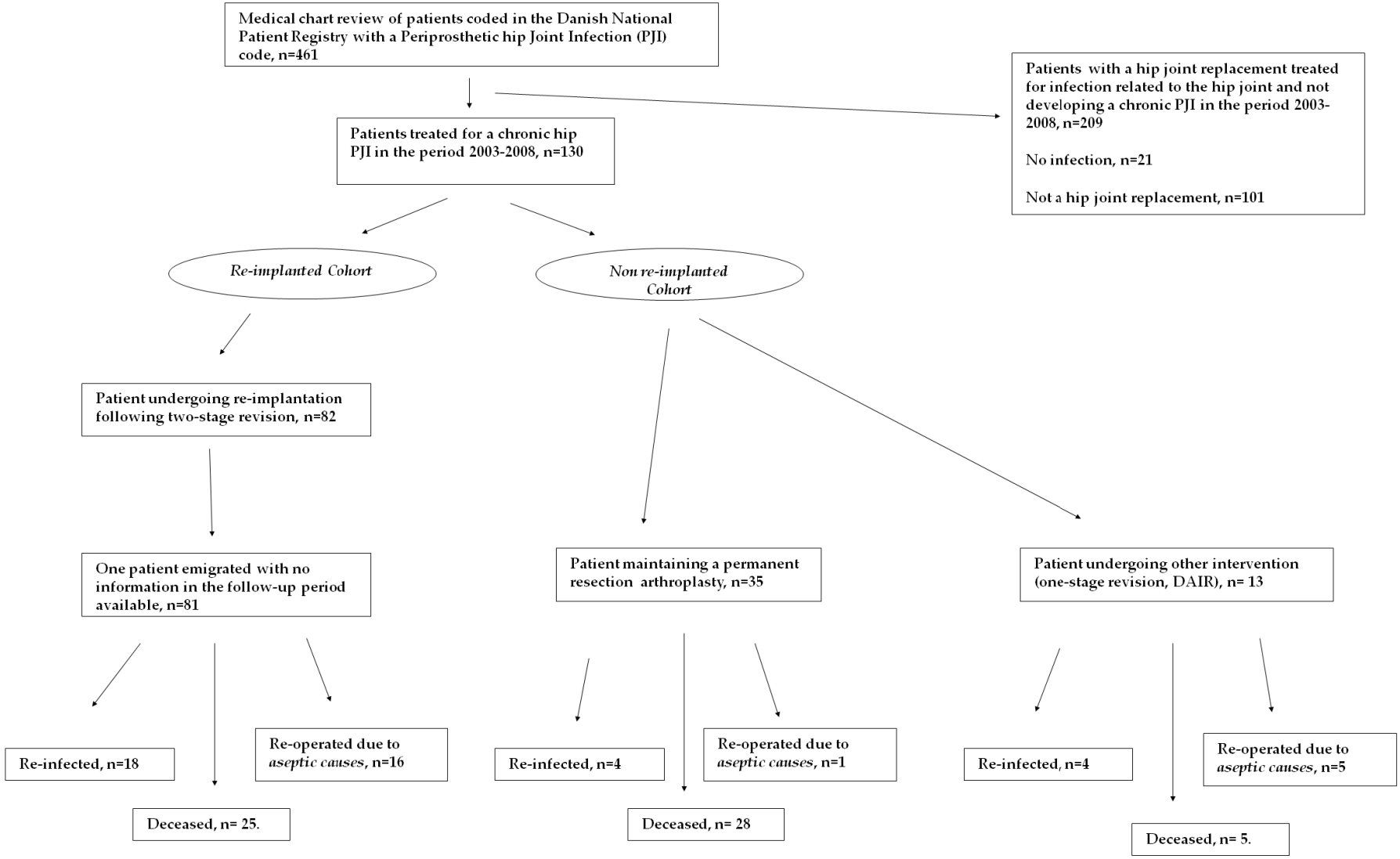


Figure 7.
Flow-chart for patient included in study III

Ethical Aspects

All work of this thesis was done in accordance with the ethical rules denoted in the Helsinki declaration.
Study approval was obtained from The Danish Health and Medicines Authority in study II & III ((3-3013-129/1/KAHO) and from the Danish Data Protection Agency in study II & III (2010-41-4294).

Outcome Parameters

Our primary endpoint across all studies in the thesis is re-infection.
Re-infection remain the most dominant outcome parameter chosen, for primary endpoint analysis after revision procedure in chronic hip PJI.
In study II & III we applied our classification system, to the event of (re-)infection, in an effort to ease comparison and extrapolation of findings to those of others.
We defined a category A infection as one, where a fistula to the joint was present.
A category B infection was one, in which a relevant per-operative tissue biopsies, using standardized sampling technique, would identify a relevant micro-organism (in Denmark by applying the Kamme and Lindberg principle[28]).
A Category C infections was an infection based on clinical inference of findings, that could relate in some perspective, to the existence of an infection. This could be elevated infection serological markers, such as C-Reactive Protein (see figure 9).

Definition of periprosthetic hip joint infection (PJI):
Category A PJI:
Fistula
Category B PJI:
Positive intra-operative cultures
Category C PJI:
Positive pre-operative cultures from joint fluid aspiration
and
Visual pus or purulent fluid during revision procedure
OR
one of the above with clinical signs of infection (one or more of the following):
- Positive Indium-111 "white blood cell" bone scan
- C-reactive protein above normal (regardless of numerical value) OR erythrocyte sedimentation rate > 30 mm/hour
- Suspicious conventional radiography
(periostitis and cortical thickening, endosteal cavitation of the femur, cloacae in the femoral cortex or migration of implant)

Figure 9.
Periprosthetic hip joint infection categories.

Secondly, we also evaluated patient mortality and open aseptic revisions performed after re-implantation.
Whether or not patients die during follow-up, by treatment related or non-related causes, is important in the evaluation of the prognosis[109].
Mortality may cause a statistical impact on outcome estimates[160], although the clinical significance of this in HJR remain debated[161].
Mortality assessment is easily done in Denmark, due to the mandatory registration of causes of death, to the administrative death register, maintained by the Danish Health and Medicine Authority. The register includes time of death, and can be linked via the CPR number. The electronic medical records are automatically updated on this information, and use of a patients CPR number determines the vital status of that patient.
As most deaths in Denmark occurs at hospitals, at nursing homes or during hospice stay, and that all deaths, by law, has to be registered by a medical doctor, with undisputable patient identification, only rare cases eludes the system, for instance by emigration.
In study III mortality assessment by all-cause mortality was integrated in the statistical analysis. In study I, this information was not available. The exact cause of death was not determined.

Registration of further surgery to the hip is also relevant, to enable a full evaluation of the beneficial nature of revision strategies. Dislocation, early periprosthetic fracture or late aseptic loosening may differ among the chosen techniques. And all open revision procedure, done after the index re-implantation, will affect the risk of re-infection, the function of the joint, and patient satisfaction. The local medical records are a reliable source of further procedures performed at that hospital, but cannot give insights into procedures performed at other hospitals. In Denmark, due to the free and universal health care coverage, patients may have treatments performed at many locations. To cover this, *e-journal* was used in conjunction with the local medical records, which allowed nationwide information on further treatments performed.

Analytic Considerations

One can analyze data from observational longitudinal studies in many way[162]. Cumulative incidence estimates, the proportion of individuals having the outcome of interest in a specific time period[163], is an easily interpretable way of portraying results, but comes at a cost. They may be incomplete, or clinically flawed, as patients lost for all-causes during follow-up, may influence our interpretation[109]. One study reported a cumulative incidence of re-infection of 4% within a few years of follow-up[92], but not all patients had survived the follow-up period. These, where not taken into account in the analysis. Had all patients in the case-series, by chance, died during the defined follow-up period, the risk of re-infection would still be 4%. It may make sense from a clinical perspective, when the surgeon is "only" interested in the patients, he might face again, so he can advice his patients that only 4% will need surgery again due to re-infection[161,164]. But, from an overall point of view, this is a limited-value advice[109].

Information on the progression of the outcome are not available in a "standard" cumulative incidence analysis, and many paths can lead to the same estimate[165]. Also, some patients may be followed for a longer duration, than the used time frame, and this information is not used. Adding to this, the rate of events occurring may not be constant in time[163], e.g. the rate of re-infection is high in the first couple of years after surgery and then flattening out(III), or the rate may differ between compared study groups. To optimize the use of all available information, and appropriately handle a non-constant rate[163], time-to-event analysis should be performed, the most well-known, and applied, method being the Kaplan-Meier survivor function. In the Kaplan-Meier analysis, it is assumed, that patients censored have the same risk of developing the outcome, as those not yet censored (independent censoring). A deceased patient should still be at risk of developing re-infection, which is evidently wrong, as dead patients cannot develop a re-infection[166].
In order to avoid bias to the time-to-event analysis introduced by this censoring, competing risk analysis, treating death and/or other relevant variables as competing events, could be applied to the data[160]. Although the absolute mathematical difference may not appear large in studies on hip PJI(III), or in joint replacement register studies[161], performing a Kaplan-Meier analysis is statistical erroneous[160,166].
However, the clinical aspect of this is debated. An introduction to analysis of arthroplasty data obtained from registers, have been published by the Nordic Arthroplasty Register Association study group in 2011[161,164]. They gave an example of the biased estimate in a theoretical setting, and calculated an 25% overestimation of the incidence by the Kaplan-Meier analysis (a 20% risk vs. a 25% risk). But, an argument was made, that from a clinical perspective, the Kaplan-Meier analysis may be more appropriate, given the fact that patients (or physicians) is only interested in events occurring during the patient's lifetime. They do not, however, comment on the application in studies comparing groups in low-prevalence conditions, such as hip PJI, with potential co-existence of immortal person time bias and other confounders.
Although statistically appropriate, whether competing risk analysis in this aspect is clinical relevant, has not been investigated.

In one-stage revision, the aspect of censoring by death, may theoretically impact an overestimation of the cumulative incidence, by the Kaplan-Meier method. More so, than in a two-stage revision, due to the potential immortal person time in the interim period[109], influencing any comparison made between these two strategies, in favour of two-stage revision[166,167].

The performance of meta-analysis on data obtained in systematic reviews remain debated, as do the value of the synthesis[168,169].
However, much of the concern involves the rigor, to which collection of data is performed[170,171], and the heterogeneity existing among the studies, from which data was extracted.
As in our analysis(I), data may be extracted on sub-groups of patients, with relevant data on the topic of interest. Yet, the primary purpose of the author of the native study, may have been completely different, and affected inclusion of patients, and such different studies make up the available pool of patients being included.
This introduces heterogeneity, which can severely affect the synthesized summary effect estimates obtained in the meta-analysis[172,173].
One way to acknowledge this aspect, is to perform a random-effects model analysis[172,173]. The random-effect model does not assume the presence of a single "true" effect size across all studies, but assumes that each individual study has its own "true" effect size, thus limiting the impact of this heterogeneity. In essence, all meta-analysis should be performed using a random-effects model. Yet, performing a random-effects model, do not remove the responsibility of the investigators, to critically evaluate heterogeneity on the synthesized summary effect estimates.
Several statistical software exists in which to perform meta-analysis. This can be done in STATA (STATA corp. College Station, TX), RevMan (Review Manager. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) or in the software used in this study (Comprehensive Meta-Analysis. Biostat inc. Englewood, NJ).
As the software used in our study I had been limited applied to published literature, we had the synthesised summary effect estimates and meta-regression tested against STATA performed by a biostatistician from the Department of Clinical Epidemiology, Aarhus University Hospital, upon acceptance for publication. Incorporating the fact that the soft-ware used for our meta-analysis adds a 0.5 to the numerator in the case of zero events in a risk estimate, the soft-ware showed equality to STATA in outcome calculations.

Statistical Methods

Due to the nature of design of the studies in this thesis no sample size calculations were performed.
Descriptive statistics were calculated as proportions with 95%CI in case of dichotomous outcome, means with 95%CI in normal distributed continuous outcome, and medians with IQR in case of skewed continuous or categorical outcome.

We evaluated data graphically to assess normal distribution by Q-Q plots in study III; the Proportional-Hazards assumption by log-log plots in study III; the presence of publication bias by funnel plots in study I.

We estimated the main outcome of study I+II as simple proportions with 95%CI.

As we expected heterogeneity to be present among the identified studies in study I, we used random-effects modeling[172].

We performed competing risk analysis to estimate the cumulative incidence of the main outcome in study III[160,174]. We believed death and open aseptic revision to be competing events regarding the primary endpoint of re-infection.
The Kaplan-Meier method was used to estimate survivor function in study III.
Due to immortal person time bias in the two-stage group in study III, we estimated time-at-risk from date of re-implantation and not from removal of index HJR in this group. Sensitivity analysis did not detect influence of this bias on study conclusions.

In comparison between groups, chi-squared test was used in case of binary data, T-test for normal distributed continuous data, rank-sum test for skewed continuous or categorical data, and Log-rank test for survivor functions.
We fitted regression models to examine selected predictor variables influence on outcome. We applied in-software, meta-regression in study I, and fitted Competing-risk regression model (Fine & Gray) and Cox regression model in study III.

The level of statistical significance was accepted at $p<0.05$, with no Bonferroni adjustment made in the case of multiple-comparison testing, as none of the studies *a priori* defined a null hypothesis and by study nature were hypothesis-generating.

Data analysis software used was Comprehensive Meta-Analysis 2.0 (Biostat inc. Englewood, NJ) in study I and STATA 11.2 (STATA corp. College Station, TX) in study II & III.

Summary of Results

Study I

We identified 1304 patients with a relevant follow-up description in the included 36 studies.

These patients underwent re-implantation following either a one-stage revision (n=375) or a two-stage revision (n=929). We did not find a difference in age or gender between the two groups, but the lack of reporting and essentially the quality of data on comorbidity, ASA score, BMI and other relevant risk factors did not allow us to correct for these.

We found the risk of re-infection of the 1304 patients to be 11.3 % (95% CI; 9.6 %– 13.2%). The risk of re-infection following re-implantation in a two-stage revision was 10.4 % (95% CI; 8.5 % - 12.7%) and following re-implantation in a one-stage revision 13.1 % (95% CI; 10.0 % -17.1 %) (see figure 10).

Group by Type of operation	First Author	Event rate	Lower limit	Upper limit	Total
one-stage	Ure 1998	0,024	0,001	0,287	0 / 20
one-stage	Mulcahy 1996	0,031	0,002	0,350	0 / 15
one-stage	Drancourt 1993	0,045	0,003	0,448	0 / 10
one-stage	Rudelli 2008	0,071	0,004	0,577	0 / 6
one-stage	Rudelli 2008	0,077	0,019	0,261	2 / 26
one-stage	Callaghan 1999	0,083	0,021	0,279	2 / 24
one-stage	Yoo 2008	0,083	0,012	0,413	1 / 12
one-stage	Hope 1989	0,125	0,066	0,223	9 / 72
one-stage	Lai 1996	0,143	0,020	0,581	1 / 7
one-stage	Raut 1995	0,158	0,112	0,219	29 / 183
one-stage	COMBINED	0,131	0,100	0,171	44 / 375
two-stage	Fink 2009	0,014	0,001	0,182	0 / 36
two-stage	Cordero-Ampuero 2009	0,024	0,001	0,287	0 / 20
two-stage	Buttaro 2005	0,034	0,005	0,208	1 / 29
two-stage	Hofmann 2005	0,037	0,005	0,221	1 / 27
two-stage	Yamamoto 2003	0,045	0,003	0,448	0 / 10
two-stage	Walter 2007	0,050	0,013	0,179	2 / 40
two-stage	Isildar 1999	0,050	0,003	0,475	0 / 9
two-stage	Lai 1996	0,053	0,007	0,294	1 / 19
two-stage	Magnan 2001	0,056	0,003	0,505	0 / 8
two-stage	Nusem 2006	0,056	0,008	0,307	1 / 18
two-stage	Scharfenberger 2007	0,056	0,003	0,505	0 / 8
two-stage	Takigami 2009	0,056	0,003	0,505	0 / 8
two-stage	Dairaku 2009	0,063	0,004	0,539	0 / 7
two-stage	Sanchez-Sotelo 2009	0,071	0,041	0,122	12 / 168
two-stage	Koo 2001	0,083	0,012	0,413	1 / 12
two-stage	Wang 1997	0,091	0,023	0,300	2 / 22
two-stage	Fehring 1999	0,091	0,023	0,300	2 / 22
two-stage	Cabrita 2007	0,091	0,038	0,200	5 / 55
two-stage	Whittaker 2009	0,093	0,035	0,223	4 / 43
two-stage	Lieberman 1994	0,094	0,031	0,254	3 / 32
two-stage	Lim 2009	0,118	0,045	0,275	4 / 34
two-stage	Stockley 2008	0,123	0,074	0,197	14 / 114
two-stage	McDonald 1989	0,136	0,077	0,229	11 / 81
two-stage	Tsukayama 1996	0,147	0,063	0,308	5 / 34
two-stage	Nestor 1994	0,176	0,081	0,341	6 / 34
two-stage	Hanssen 2002	0,176	0,058	0,427	3 / 17
two-stage	Incavo 2009	0,182	0,046	0,507	2 / 11
two-stage	Evans 2004	0,273	0,090	0,586	3 / 11
two-stage	COMBINED	0,104	0,085	0,127	83 / 929
Overall	COMBINED	0,113	0,096	0,132	127 / 1304

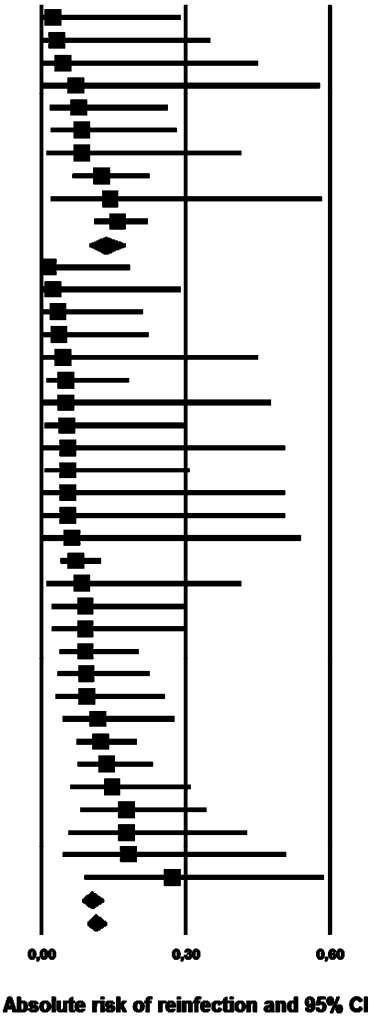


Figure 10.
Forest plot illustrating the absolute risk of re-infection following the different revisions procedures.

The only study variable indicated by regression modeling to correlate with a lower risk of re-infection was the age of publication, in which newer publications showed better results (p-value 0.02).
As expected we identified only few studies with high re-infection risks, indicating publication bias.

Study II

We classified 240 patients as true hip PJIs in the 283 patients identified with a T84.5 ICD-10 discharge diagnosis code. This corresponded to an overall positive predictive value of 85% (95%CI 80-89).
In patients with a T84.5 ICD-10 discharge diagnosis code in combination with an infection-specific procedure code, the positive predictive value was slightly higher than the overall positive predictive value; in patients with a T84.5 ICD-10 discharge diagnosis code in combination with a noninfection-specific procedure code the positive predictive value was slightly lower (86%, 95%CI 80-91 and 82%, 95%CI 72-89 respectively).
If patients had a fistula at time of revision, or had positive per-operative tissue biopsies, they were more likely to be coded correct.

Study III

We divided the 130 identified patients into two groups based on the revision strategy chosen. 82 patients constituted one group and was characterized by having a re-implantation performed in a two-stage revision. The remaining 48 were not treated using a two-stage revision. The two groups did not differ in the registered peri-operative parameters of the initial procedure. However, we found a significant baseline difference in selected patient variables indicating that the patients in the two-stage re-implantation group was younger and had better overall health , as indicated by the surrogate health markers, ASA and CCS (see table1+2).
8% of the patients died within 1 year and 32% within 5 years (see figure 11).

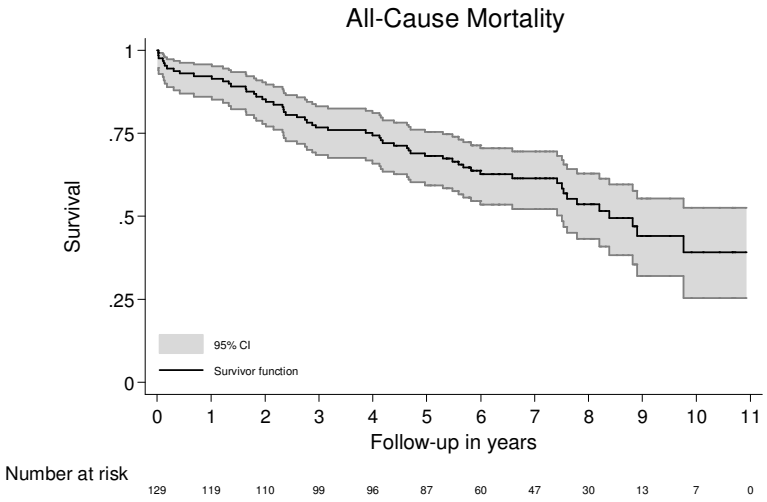


Figure 11. Kaplan-Meier Survival curve for 130 patients.

Table 1. Baseline demographics of 130 patients treated for chronic hip PJI between 2003-2008.

Variable	Overall Cohort	Re-implanted	Non-reimplanted	p-value
Age in years Mean (95%CI)	71 (69-73)	68 (66-71)	76 (72-80)	0.0006
Age at time of death in years Mean (95% CI)	80 (77-83)	77 (73-81)	82 (79-86)	0.05
Male gender % (95%CI)	51 (42-59)	57 (46-68)	40 (26-55)	0.07
Excessive Alcohol consumption* % (95%CI)	10 (4-15)	12 (6-22)	4 (1-15)	0.16
Smoker % (95%CI)	26 (19-34)	25 (15-35)	29 (15-42)	0.64
Antithrombotic treatment % (95%CI)	30 (22-39)	32 (21-42)	29 (16-42)	0.76
SIRS at time of initial procedure˜ % (95%CI)	3 (0-6)	1 (0-4)	6 (1-13)	0.11
Index HJR is a revision prosthesis % (95%CI)	25 (17-33)	25 (15-35)	24 (11-37)	0.86
Number of prior operations to index hip Median (IQR)	2 (2)	2 (2)	2 (2.5)	0.06
CCS Median (IQR)	0 (1)	0 (1)	1 (2)	0.005
In situ duration of index prosthesis in weeks Median (IQR)	89 (204)	88 (191)	91 (370)	0.73
BMI in kg/m² Mean (95% CI)	26.0 (25.0-27.0)	26.9 (25.7-28.0)	24.4 (22.8-25.9)	0.005
BMI groups % (95%CI)				
<18.5	4 (0-7)	4 (0-8)	5 (0-11)	0.001
18.5-25	46 (37-54)	33 (23-44)	68 (54-82)	
25-30	29 (21-38)	40 (29-50)	11 (2-21)	
>30	21 (14-28)	23 (14-33)	16 (5-27)	
Pre-operative hemoglobin in mmol/l Mean (95% CI)	7.3 (7.1-7.5)	7.6 (7.4-7.8)	6.8 (6.5-7.2)	0.0004
ASA score Median (IQR)	2 (0)	2 (0)	2 (1)	0.0001
Follow-up in years Median (IQR)	8 (3)	7.9 (3.1)	8.7 (3.5)	0.03

SIRS: Systemic Inflammatory Response Syndrome; CI: confidence interval; IQR: Interquartile Range; ASA: American Society of Anesthesiologists score; BMI: Body Mass Index; CCS: Charlson Comorbidity severity score; HJR: Hip Joint Replacement;

* More than 21 units/week for men and 14 units/week for women.

˜ 2 or more of: temperature >38.0/<36.0, Heart rate >90/min, Respiratory Frequency >20/min, White blood cell count >12.0x10^9/<4.0x10^9

Table 2. Peri-operative variables of 130 patients treated for chronic hip PJI between 2003-2008.

Variable	Overall Cohort	Re-implanted	Non-reimplanted	p-value
Femoral osteotomi performed % (95%CI)	48 (39-56)	52 (41-63)	38 (24-52)	0.12
Stem loose % (95%CI)	22 (15-29)	28 (18-38)	11 (2-20)	0.02
Cup loose % (95%CI)	28 (19-36)	22(12-31)	40 (23-57)	0.05
Duration of surgery at initial procedure in minutes mean (95%CI)	148 (137-159)	156 (141-170)	133 (115-151)	0.05
Blood loss at initial procedure in liters mean (95%CI)	1.7 (1.5-1.9)	1.8 (1.6-2.1)	1.6 (1.3-2.0)	0.42
Anesthesia **General** **Spinal** **Other** **% (95%CI)**	 58 (49-66) 41 (33-50) 1 (0-2)	 57 (46-68) 42 (31-53) 1 (0-4)	 60 (45-74) 40 (26-55) No obs.	0.72
Neurological deficits in the ipsilateral extremity following index treatment % (95%CI)	2 (0-4)	2 (0-6)	No obs.	0.30
Blood transfusion following index treatment % (95%CI)	92 (87-97)	91 (85-95)	94 (86-100)	0.63
Number of blood transfusions median (IQR)	4 (3)	4 (3)	4 (5)	0.75
Length of stay following index treatment in days median (IQR)	25 (23)	25 (27)	24 (21)	0.67

Abbreviation: CI: confidence interval; IQR: Interquartile Range

Patients not re-implanted in a two-stage revision had a crude 68% higher risk of dying in the follow-up period compared to patients undergoing two-stage revision (see figure 12).

After adjusting for selected confounding variables the risk of dying remained 25% higher, although this was not found to be statistically significant. Poor health status, higher age, and underweight were found to be independent predictors of mortality in the established population.

The 5-year cumulative incidence of re-infection was not significantly different between the groups, and was calculated for the 130 patients to be 14.7 % (95%CI 9.3-21.4) (see figure 13A-C).

In the established population, no uni-variate predictors of re-infection were identified, and after adjusting for selected patient variables, female gender appeared to be associated to a higher rate of re-infection, as the only variable.

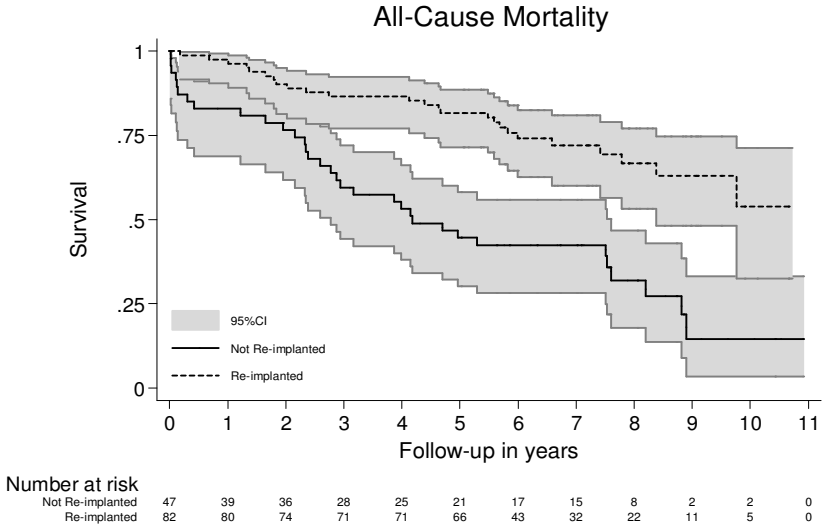


Figure 12. Kaplan-Meier survival curves for patients re-implanted in a two-stage revision compared to those not.

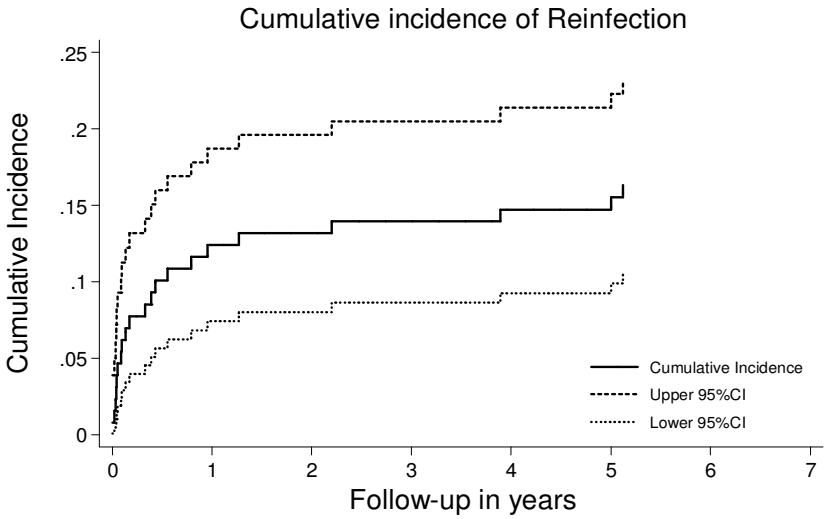


Figure 13A.
Cumulative incidence of re-infection in all 130 patients.

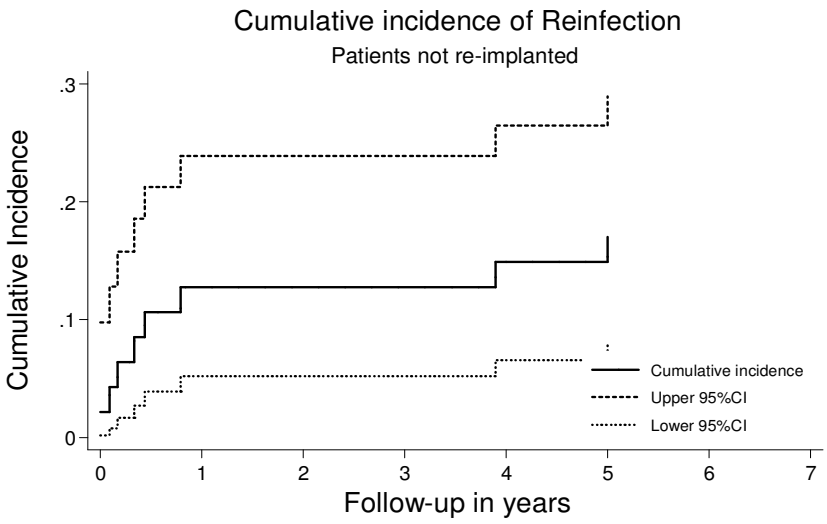


Figure 13B.
Cumulative incidence of re-infection in patients not re-implanted in a two-stage revision

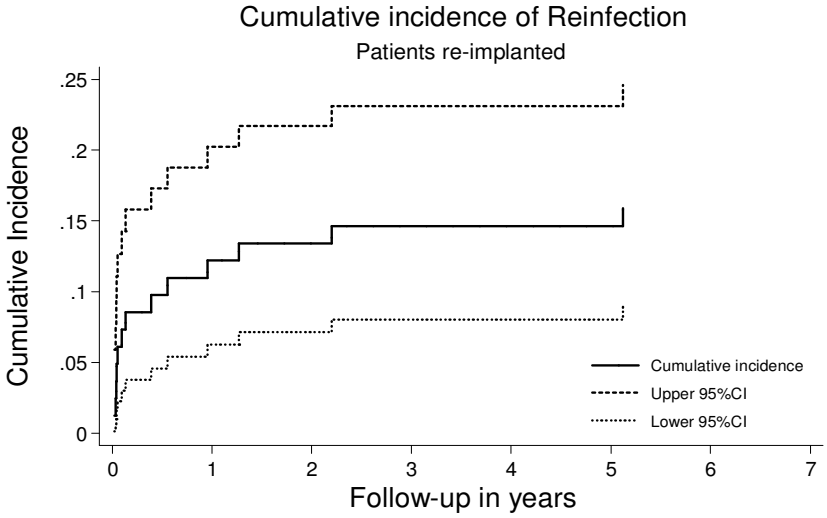


Figure 13C.
Cumulative incidence of re-infection in patients re-implanted in a two-stage revision.

Overall Conclusions

Clinical studies on outcome following hip PJIs is hampered by the relative lack of patients, and the wide diversity of demographic and clinical factors encountered in single-center research. To obtain better, more accurate, results, different strategies can be utilized.
A systematic review of current literature gathers available information, and by meta-analysis, perform statistical inference on this (I). We found a slight increased risk of re-infection following one-stage revision compared to two-stage revision. This must, nonetheless, be interpreted in light of poor general study methodology, and statistical imprecision.

Another way of obtaining large sample data is via administrative single-source registers(II). This could be a potential valuable source of information in hip PJI. But erroneous registration must be taken into consideration, as only 85% of patients coded with a relevant ICD-10 discharge diagnosis code, actually represents a hip PJI. We still believe administrative registers to be useful in studies on outcome following treatment for hip PJI, but misclassification must be taken into consideration, when interpreting results from such.

Multi-centre, longitudinal studies is another feasible path to a larger sample size(III). However, in hip PJI, it is a time/labour consuming way of performing research. Yet, our results are comparable to single-centre studies, and contain a considerable larger sample than would have otherwise been included in the same time frame. We found a cumulative incidence of re-infection just below 15% in the follow-up period(III), which took into account patients dying or having open surgery performed prior to a re-infection as competing events. In longitudinal outcome analysis, we believe that competing risk analysis is recommendable, although the clinical significance of performing this analysis is debated(III).
Periprosthetic hip joint infection appears to correlate to a high mortality incidence, but causality remains to be established(III).
Related to the two former, we believe selection bias do exist, favoring the presented two-stage revision cohorts (I+III), and that this is an aspect to take into consideration when comparing different treatment procedures.

Discussion

Study I

To obtain knowledge of what have previously been done, and how this affects our patients. And to incorporate this knowledge in clinical practices is a fundamental aspect of evidence based medicine. To do so, reviewing published literature is obligatory.

We wanted to investigate whether a one-stage or two-stage revision following chronic hip PJI were the most appropriate choice of treatment strategy, as no review had done this before. We were not able to identify a clear difference between the revisions strategies, regarding clinical outcomes in the available published literature(I).

This was in contrast, to the latest review on one-stage revision of hip PJI by Jackson et al[103], published in 2000. This review concluded, that one-stage revision was not an appropriate method of treatment of chronic hip PJI. The authors based their conclusion on 1299 identified patients in 12 studies. These were identified via a single database search (Pubmed), and restricted to English language publications.

A 83% clinical success incidence was found, which was actually not that different from the 87% estimated in our study(I).

But the conclusion drawn by Jackson et al, lacked a direct comparison to two-stage revision, and were of narrative nature.

Of the 12 studies included in the Jackson review, only two[129,130] were repeatedly used in our review. Noticeably, we did not include the study of Buchholz[99], due to a lack of relevant patient information. This particular study had a very important impact on the conclusions drawn in the Jackson review, as the study reported a 77% clinical success incidence, and constituted nearly half of all patients in the review.

We also questioned the appropriateness of this review, as only studies in English were included. Due to the fact, that the Endo-Clinic in Hamburg, Germany was the original site of one-stage revision, relevant studies may have been published in German. As it turned out, we only indentified 1 study in German, which could be included in our meta-analysis(I).

Two other systematic reviews has been published comparing one-stage to two-stage revision. Both using strict criteria for study inclusion, and application of a search strategy to both Pubmed and Embase.

In the 2014 review by Leonard et al[106], studies were only included, if directly comparative between revision strategies, as opposed to our inclusion of single-arm series(I).

9 studies were included, of which only Hope[129] were included in our review.

A 16.8% and 10.6% cumulative incidence of re-infection was found in the one-stage and two-stage groups respectively, but as confidence intervals were overlapping, the two-stage strategy could not be determined superior.

Also this review was severely limited by the confounding by indication introduced in the included comparative studies, as none were randomized trials, and furthermore no apparent discrimination of acute or chronic infections were performed in the review.

The same year as our meta-analysis, Beswick et al[108] published a systematic review, investigating re-infection within 2 years of follow-up, in studies with more than 50 cases.

They included 11 studies on one-stage revision with 1225 patients, and a 8.6% cumulative incidence of re-infection and 28 studies on two stage revision with 1188 patients and a cumulative incidence of re-infection of 10.2% .
Again, overlapping confidence intervals made it impossible to conclude on the superiority of either treatment strategy. Of the studies in this review, 4 one-stage revision and 10 two-stage revision publications were also applied to our analysis(I).
The conclusion drawn in the two latter reviews was in line, with that established by our analysis(I). Cumulative incidence of re-infection following treatment for chronic hip PJI, regardless of revision strategy, is approximately 10%. Even with the quite large number of studies, the pooled cumulative incidence estimates were all found to be statistically imprecise. There is an apparent lack of well-conducted studies, that once-and-for-all establish which revision strategy is superior, if any, and to whom either should be applied. To summarize the best available information to date, from 3 systematic reviews which spans more than 4 decades of published literature, information is insufficient to make conclusions.

Study II
Register studies enable large samples, compiled from many centers and surgeons, and are as such a valuable asset in evaluation of treatment.
Registers can be administrative (e.g. DNPR) or clinical (e.g. the Danish arthroplasty registers).
Administrative discharge registers enables on a very large scale, the acquisition of information on treatment and disease. This enables projections to be made, on both incidence and prognosis. Such administrative register have been used frequently on evaluation of HJR[4,13,35,40,46,175-177]. This research primarily originates from the USA, by use of The US. Medicare 5% sample claim database or the US. National Hospital Discharge Survey. In Denmark administrative registers can easily be linked to other registers by way of the CPR number system, and we wanted to investigate, whether the main medical administrative register, the DNPR, could be applied in register based research on hip PJI. At the initiation of this study in 2010, no publications had, to our knowledge, ever evaluated the discharge diagnosis codes following hip PJI. But during the writing of this thesis, 3 studies by Calderwood et al has come to our attention[178-180]. In 2012[180], this group published an evaluation of claims to Medicare for optimizing identification of surgical site infections (SSI), not specifically hip PJI. Claims coded with a wide variety of ICD-9 discharge and procedural codes relating to SSI were identified, and medical records reviewed, of which only 71% were available. The diagnosis of SSI was based on the *Center of Disease Control* criteria[181], and included both superficial, deep and space SSI. The authors concluded, that administrative registers can be used in identifying SSI for national surveillance purposes. In 2013[179], the authors used an optimized search strategy established in the 2012 study, to identify a random sample of 1000 patients primary hip arthroplasty. Information were available on 628 patients, of which 175 had deep or space SSI and 76 had superficial SSI. These data was used to construct a search algorithm, that allowed Medicare claims to be used to identify hospitals with high SSI risk.

In 2014[178] the authors extrapolated their 2013 findings, to the 175 patients identified with deep/organ SSI. The aim was to identify and optimize a search strategy, that allowed inclusion of all relevant SSI (high sensitivity), with as high a positive predictive value as possible. The authors also identified, in this selected Medicare sample, the positive predictive value of the ICD-9 code 996.66, which are identical to the ICD-10 code T84.5. They calculated a 80% positive predictive value, and a sensitivity of 82%. The positive predictive values of our two studies are very uniform, despite the difference in patient sampling and infection definition. And the high sensitivity of the code, suggest that a vast majority of hip PJI will be identified, if we accept the notion that Medicare surgeons and Danish surgeons code uniformly.

As the DNPR is a valuable research register, other studies have investigated the predictive values of discharge codes in here. Diagnosis by simple laboratory measurements should be straight forward, and the coding of these diseases in administrative registers performed without erroneous registration. However, this is not so[182,183]. Holland-Bill et al[183] investigated the coding of hyponatraemia in the DNPR, and compared the discharge diagnosis coding of this event to a "gold standard" serum sodium measurement recorded in a laboratory research database. Based on more than 2 million hospitalizations, the authors found a surprisingly "low" positive predictive value of only 92.5%.

This means that 1 in 10 patients, coded for hyponatraemia in the DNPR, may not have this electrolyte disturbance, and the cause to this erroneous registration unknown.

Even though, this for epidemiological research purposes is a strong predictive value, the erroneous registration of a seemingly simple diagnosis is noteworthy.

This issue has also been confirmed by Zalfani et al[182]. The authors investigated discharge diagnosis codes for anemia in more than 3300 patients, and again compared to a "gold standard" hemoglobin measurement recorded in a laboratory research database.

They found a positive predictive value of 95.4%, and discussed this as a matter of the physician upon previous anemic episodes, still considering the patient anemic, even though subsequent measurements shows *cross-sectional* normal values.

Hip PJI is a complex diagnostic entity. In disease, with complex diagnostic criteria, one can better accept, that discharge diagnosis codes is based on a more empirical registration, as it is seen in acute stroke, acute coronary syndrome, atrial fibrillation and flutter, infection among cancer patient, infant respiratory distress syndrome and venous thromboembolism[184-189], and that evaluation of the positive predictive value is also based on empirical criteria, defined by the investigator. It is nevertheless obvious, that discharge diagnosis codes in administrative discharge registers are subject to erroneous registration on many levels, and that this must be taken into consideration on a study-to-study basis[190].

We believe, that our study indicate single-source administrative discharge registers as a useful way of obtaining large-sample data on aspects related to hip PJI. But note, that misclassifications (discussed further below) on all levels of exposure and outcome, must be taken into consideration when interpreting results based on such registers. We believe the established positive predictive value to be a worst-case value. We do not feel discourage by this, and believe the ICD-10 code to be of value in future studies.

Study III

As no high quality comparative studies exist, that evaluate a one-stage revision compared to a two-stage revision in matched cohorts, and that this may not be clinical feasible[25] with the projected inclusion of more than 3000 patients, we need to examine other ways to enable better comparison of single-arm studies.

One way to ensure this, is more elaborate information on selection of patients in the single-arm studies, and the evaluation of the prognosis of non-selected groups, to determine the potential degree of confounding by indication (surgical selection bias).

Proponents of the one-stage revision has highlighted, that a two-stage revision allows for a "double" control before re-implantation. Patients scheduled for re-implantation, who by all causes, do not become re-implanted, may bias the results presented in literature. Technically, the interim period also allows for multiple debridement attempts before a re-implantation, which is not available to a one-stage revision.

We found in our sample, that only 63% of patients had a re-implantation following a two-stage revision procedure, and among those not re-implanted in a two-stage revision, 65% had died within 5 years. Others describe re-implantation rates of up to 92%[96,109,111] or simply do not state it[92,93]. Rarely are the patients not re-implanted sufficiently described. This could be interpreted as the existence of surgical selection bias in the comparisons made between two-stage revision and one-stage revision [25,106,108].

Currently very limited information is available, on the outcome of non-selected samples of patients with chronic hip PJI[150]. We established a non-selected cohort of patients being surgically treated for a chronic hip PJI, and examined the prognosis of these patients. Patients re-implanted in a two-stage revision differed from those not re-implanted in a two-stage revision by being younger and healthier clearly indicating a clear selection.

We also established an overall high mortality in our sample. More than 50% of patients had died within 8 years of follow-up. Unfortunately, we do not have the cause of death, nor have we compared our sample to a matched background population, so a clear correlation cannot be established. But others have commented on the potential correlation between patients with a hip PJI and mortality rates [109-111]. Mortality rates up to 48% at 5-year follow-up have been reported, and significantly different in comparison to aseptic revisions[111]. Mortality may also bias results between treatment strategies on different levels. Berend et al has recently highlighted one aspect of this, and concluded that control of infection is not achieved, if a patient is not re-implanted, due to all causes, and that future reports should include such a "worst-case" scenario[109]. We believe this to be a valid point. Whether patients are selected for a treatment strategy, due to co-morbidities or risk of dying at the time of decision, or that patients simply die before offered a chance for re-implantation is beyond the scope of this thesis. But it is indicated in our study, that patients re-implanted has a lower risk of dying compared to those not re-implanted (see figure 12).

And this overall confounding by indication must be taken into consideration when comparing different treatment strategies.

Another way to better compare results from single-arm studies, are by optimizing the statistical analysis. We chose to investigate the outcome of re-infection(III) by the most appropriate method available today, competing risk analysis. We found that between 14-

15 % of patients were re-infected within 5 years, regardless of treatment performed, and doing so acknowledging competing events of death and aseptic revision.
In 2014, Zeller et al[102] published the prognosis following treatment for chronic hip PJI from a tertiary referral centre, by competing risk analysis. The vigorous treatment protocol in this centre, lead to an impressive 5% cumulative incidence of re-infection, which must set a benchmark for others to reach. Yet, remembering this being a highly-specialized tertiary referral centre, and that this low cumulative incidence could be attributed to patient selection and analytic strategy, as compared to other studies reporting on a one-stage revision. Our results are nevertheless directly comparable by nature of analysis, and do emphasise the need to improve the prognosis of Danish patients, even after a two-stage revision. The cumulative incidence of re-infection from the study of Zeller et al and ours are also uniform, as death and open aseptic revision is taken into account. In one-stage revision, the aspect of censoring by death, may theoretically impact an overestimation of the cumulative incidence, by the Kaplan-Meier method. More so, than in a two-stage revision, due to the potential immortal person time in the interim period[109], influencing any comparison made between these two strategies in favour of two-stage revision[166,167]. Although statistically appropriate, whether competing risk analysis in this aspect is clinical relevant, has not been investigated.
One of the values of time-to-event analysis on data from longitudinal studies is the possibility of evaluation of information obtained in the entire follow-up period.
By inspection of figure 13A, it is clear that the majority of patients develop re-infection within the first two years post-operatively. This trend is also found by others[102]. This indicates that the often used "minimum" follow-up period of 2 years following treatment for chronic hip PJI is a relevant time frame[93,109].

Methodological Concerns
All studies in this thesis have the uniform primary endpoint of re-infection.
This is the most used endpoint, evaluating hip PJI. But what is a re-infection?
The MSIS criteria, and the categorical definition used in study II & III, are a mixture of pre- and per-operative diagnostic, more or less invasive in nature.
Although it has been well established, that serological markers of C-reactive protein and Erythrocyte Sedimentation Rate can be used to *rule-out* infection, we still need highly accurate non-invasive methods of *rule-in* re-infection.
Patients included in the studies used in our meta-analysis(I), our register study(II) and our observational studies(III), all have in common, that establishing re-infection in a chronic hip PJI is often based on a stepwise process.

- First the patients go to a family physician, due to a hip problem severe enough, that it warrant further exam. Which may not be the same in a nursing home resident or active golfer.
- Secondly, being referred by the family physician, who actually considers the problem to arise from the hip joint, to a relevant department of orthopaedic surgery.

- Thirdly, the surgeon upon examination of the patient suspects a hip PJI, then initiating ad hoc investigations, to increase the diagnostic likelihood of a hip PJI being the problem.
- Finally the patient is (perhaps) surgically treated, and (perhaps) deemed re-infected by per-/post-operative examination.

So, as we lack *the* gold-standard, *non-invasive* diagnostic modality, that tell us, if a patient truly is re-infected, we need to endure pragmatism, and accept that our definition of re-infection is flawed.
In essence, what we report in our studies is not, if our patients are re-infected. But if they are diagnosed and/or treated for a re-infection. Which may not be the same from study to study[25]. Focus on this will hopefully give us more uniform criteria for comparison in the future. But until then, we need to keep a critical appraisal of which outcomes we use, to be sure we are comparing uniform samples.

When performing clinical epidemiological studies being observational (e.g. register studies or case-series) or experimental (e.g. randomized controlled trials), bias is for all practical purposes inevitable. Studies on complete populations are rarely possible, and thus a "random" sample is drawn from a population. Inference on results from this sample, is then applied to the population. Is this sample truly representative of the entire population under investigation, or will it be biased (systematically skewed) in some known or unknown direction[165]? And is this sample comparable to other samples drawn from like populations? The influence of bias on the clinical inference of the presented results always necessitate a thorough evaluation[162,165].

In study I, we cannot truly state that all relevant studies were included in our review. Even though our search strategy was developed between an experienced state university librarian and the first author, previous studies have shown that search strategies are imperfect[116,118]. We adapted a systematic approach in establishing the sample[171], as an inclusion of the entire population was difficult (A go-through of all available literature in full text). But this search strategy has not been validated, and intra- and inter observer agreement was not tested. Further, we revealed the likelihood of publication bias. This indicate, that the available studies, are a selected sample from start.
It has been established, that studies with negative results are less likely published in major journals, or are merely presented on congresses, never indexed in major databases. Thus making these unavailable for systematic reviews. Also, authors of such studies are more likely to discard their work, and never publish it[191,192].
We nevertheless believe, that our study enholds a vast majority of relevant studies, based on other reviews[106,108], and our empiric knowledge of published material.
The definition of infection varied considerably in the included studies, and there is a risk that we actually compared different patient samples by adapting the pragmatic approach we did.
We initially applied a strict definition of chronic infection, but as we initiated the review we expanded our definition based on the wide diversity of interpretation of chronic

infection[87,123,150,193-198]. Inclusion into the studies, used in our review, was done at the discretion of the surgeon, as none of the studies had randomized designs, leaving a potential for confounding by indication, which could not be controlled. This subjective inclusion, left a high likelihood of assembly bias in the established cohorts. As we had no information on comorbidities, or other patient demographics to clearly establish the uniform entities of the two defined cohorts, concerns exist to the conclusion drawn from our meta-analysis. We may in reality compare apples and oranges[165,172].
Opponents of meta-analysis of low grade data, gathered in systematic reviews, often proclaim the "Garbage in- Garbage out" metaphor. It is without doubt established, that the studies within the synthesis of our summary effects, are limited by their methodological qualities. We nonetheless chose to include studies, which only reported patient information on a sample level, and not just patient level, and acknowledge the profound effect on heterogeneity, this had on our statistical analysis. We attempted to foresee this by random-effects modeling. But, we are fully aware, that our synthesis can be looked upon as waste management[172], and the summary estimate must be evaluated with this in mind. The meta-analysis nevertheless incorporates all available information, which until then, had been used in, a not less biased, narrative assessments of the value of the two revision strategies by surgeons worldwide.

In study II, we looked only at codes at one occasion (cross-sectional), during a potentially long patient treatment course. Patients may be *en route* to cure, and thus not at that exact moment perceived as infected. For example, choosing to register girdlestone situation as non-PJI, when in fact they were often associated to a two-stage revision.
We choose this approach, as we wanted to investigate the positive predictive value of the concrete ICD-10 code, and not the sensitivity[178-180], in an attempt to establish a platform for easy-to-perform, multi-register based studies.
We conclude, based on our infection criteria, that patients are *de facto* infected. But especially concerning category C PJI, this may be debatable. Gundtoft et al[34] have recently proposed a much more elaborate algorithm for confirmation of hip PJI, than the *a priori* criteria established in our study. If our study was to be performed again, utilizing such algorithm would be valuable. Also, estimation of intra-observer and inter-observer variability would have been preferable. As data was evaluated retrospectively, important information may have been absent in the medical records pertaining to the hip PJI criteria. This information bias could negatively influence the positive predictive values in our study. One must also keep in mind, that our study only enabled evaluation of surgically treated patients, as procedure codes relating to hip surgery were necessary for inclusion in the data extract.
The accuracy of the discharge diagnosis code relating to hip PJI, could only be evaluated as positive predictive values, as information needed to obtain a measure of sensitivity, specificity and negative predictive value were not available. To truly validate the discharge diagnosis codes, we need to identify all patients at the participating hospitals with a hip PJI, registered or not with a T84.5 code (sensitivity). Also to identify all patients who did not have an hip PJI and registered or not with a T84.5 code (specificity). But this was not believed feasible.

In our study population, 6 patients with osteosynthesis hip implant infection were coded with the ICD-10 code T84.5 instead of the correct T84.6 (*Infection and inflammatory reaction due to internal fixation device [any site]*)[157]. These patients may differ systematically from the core population investigated. The discharge code for hip PJI, also capture a wide range of patients from the younger patient with an acute PJI after a primary HJR, to an elderly patient with a chronic PJI in a hemi-hip replacement after a fracture to the femoral neck. This collapse in the discharge diagnosis code may influence the subsequent analysis of association between exposure variables and outcome[190]. Misclassification relate to the issue of classification errors, and to exposure as well as outcome. Misclassification can be differential, if the erroneous registration is dependent on the subject being investigated, or non-differential, if independent of the subject being investigated[190]. Theoretically, non-differential misclassification bias an association towards null and is of concern in register based studies on hip PJI. In a recent register based study on exposure variables, alcohol abuse were not found to be a risk factor for developing hip PJI[46], (crude relative risk 2.09, p-value 0.0566). If we believe alcohol abuse to be underreported by the patients, this would bias the association toward null[190]. Alcohol abuse may in fact present a risk factor for developing hip PJI, although not detected as such, due to non-differential misclassification.

Study III presents a sample of patients retrospectively identified, via the search strategy applied to study II, and the afterwards medical records review. Even though this study population represent a more non-selected population, than previously reported[92,93,96], it is still a selected population. Extrapolation can only be made to other samples of patients with a performed surgical intervention for chronic hip PJI. We also chose to divide the sample into two-groups, based on the absence or presence of a re-implantation in a two-stage revision, to evaluate the nature of the selected sample of this latter group. This gave us the problem of immortal person time bias. One group was clearly defined by the absence of death, for a long period after entering the sample. Patients dying in the interim period, could have been destined for a two-stage review, had they not died. We have no way of adjusting for this, due to the retrospective nature of the study.
We obtained information on comorbidity from the DNPR. This could potentially underestimate, the calculated CCS score estimates. The positive predictive value of the CCS score in the DNPR has previously been shown to be high[159].
The small sample size and the retrospective nature of data extracted is also a concern when evaluating the result from the study.
We used the *e-journal* for follow-up evaluation. Although registration is mandatory, completeness has never been investigated, and some departments may have delayed entry or incomplete registration of relevant procedures.
To obtain more exact information, the Danish National Patient Register and Danish Hip Register could have be investigated.
We performed adjusted regression analysis on survival and re-infection. The parameters chosen for adjusting the crude relative risk and sub-hazard ratios were based more on the empirical beliefs of the investigators, than on evidence. Whether the chosen variables are appropriate is a potential concern. Clinical inference made from the data must be

individually evaluated in terms of both multiple-comparison testing (with no Bonferroni correction), type-2 error, or misclassification.
Due to the presence of both selection and information bias in our sample, extrapolation of results needs to be done pre-cautiously. One way to overcome some of the potential confounding in a between-groups comparison can be done by propensity score matching[199], but as this study is not a real comparative design, this was not believed to contribute significantly to the conclusions.

Perspectives and Future Research

Whether to perform a one-stage or two-stage revision is still widely debated.
However, more appropriately, consideration should be, as to which patients a one-stage revision and to which patients a two-stage revision should be chosen.
It is unquestionable, that a one-stage revision is superior in terms of cost, surgical ease and benefit for the patient. However, it seems also clear, that this revision strategy cannot be performed on all patients.
Instead of debating, which is better, future research should focus on which case-mix to apply either revision strategy, as they supplement each other, rather than compete.
In this equation, other treatment options must also be considered (see figure 1).
There is evidently an urgent need for improving our knowledge on chronic periprosthetic hip joint infections.

- We need to increase our knowledge on risk factors for developing periprosthetic infections.
- We need to increase our knowledge on prognostic factors influencing outcome of treatment.
- We need to improve our knowledge on how the patients perceives the different treatments.
- We need to optimize diagnosis and definition of periprosthetic joint infections.
- We need to optimize the performances of the individual treatment strategies.
- We need to improve our understanding of the influence of biofilm on periprosthetic infections.
- We need to improve on our reporting of result following different treatment strategies.

At Orthopaedic Research Aarhus, we plan to continue research in these areas.
Besides clinical outcome parameters, patient reported outcome measures can be relevant in the evaluation of surgical procedures. Especially concerning non-life threatening diseases such as a chronic periprosthetic hip joint infection, the patients aspects on the revision procedure is important. The surgeon may deem a HJR infection free, but what does this mean to the patient. If the treatment itself renders the patient with severe post-operative pain or disability, maybe a different treatment strategy should have been applied.
We are currently processing information on PROM's from the cohort established in study III. In our study on cementless one-stage revision, we will also evaluate the revision procedure from a clinical perspective, as well as patient oriented perspective. We have applied validated generic and disease specific patient questionnaires to evaluated patient reported outcome. We have initially planned a minimum follow-up of 2 years, but has just initiated a long-term, 10-year follow-up study of the established cohort. In relation to this, we plan on establishing a research database on treatment of non-selected patients with chronic periprosthetic hip joint infection to continue surveillance on Danish patients to help determine the appropriate case-mix per treatment protocol.

We are in the process of initiating register based studies for identification of risk factors, prognostic factors, and investigate the potential correlation between periprosthetic hip joint infections and mortality. As biofilm formation occurs within hours of colonization, and micro-organism may stay dormant for years, before being activated, the boundaries for when to perform exchange procedures, must necessarily change accordingly. The clinical relevancy of this is also an area of future research, which is planned for investigation at Aarhus University Hospital. We believe this thesis has highlighted important perspectives of treatment and outcome, to help initiate forward progression towards improved patient care.

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Appendix

Doctoral and PhD Theses from the Orthopaedic Research Group, Aarhus University Hospital, Denmark; www.OrthoResearch.dk.

Doctoral Theses

Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
Kjeld Søballe, 1993. *Acta Orthop Scand (Suppl 255) 1993;54*

Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
Martin Lind, 1998. *Acta Orthop Scand (Suppl 283) 1998;69*

Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
Søren Overgaard, 2000. *Acta Orthop Scand (Suppl 297) 2000;71*

Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology
Steffen Jacobsen, 2006. *Acta Orthopaedica (Suppl 324) 2006;77*

Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
Michael Ulrich-Vinther, 2007. *Acta Orthopaedica (Suppl 325) 2007;78*

Assessment of adult hip dysplasia and the outcome of surgical treatment
Anders Troelsen, 2012. *www.OrthoResearch.dk*

PhD Theses

In vivo and vitro stimulation of bone formation with local growth factors
Martin Lind, 1996. *www.OrthoResearch.dk*

Gene delivery to articular cartilage
Michael Ulrich-Vinther, 2002. *www.OrthoResearch.dk*

The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
Ole Rahbek, 2002. *www.OrthoResearch.dk*

Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
Søren Kold, 2003. *www.OrthoResearch.dk*

Stimulation and substitution of bone allograft around non-cemented implants
Thomas Bo Jensen, 2003. *www.OrthoResearch.dk*

The influence of RGD peptide surface modification on the fixation of orthopaedic implants
Brian Elmengaard, 2004. *www.OrthoResearch.dk*

Biological response to wear debris after total hip arthroplasty using different bearing materials
Marianne Nygaard, 2005. *www.OrthoResearch.dk*

DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups
Mogens Berg Laursen, 2005. *www.OrthoResearch.dk*

Studies based on the Danish Hip Arthroplasty Registry
Alma B. Pedersen, 2006. *www.OrthoResearch.dk*

Reaming procedure and migration of the uncemented acetabular component in total hip replacement
Thomas Baad-Hansen, 2007. *www.OrthoResearch.dk*

On the longevity of cemented hip prosthesis and the influence on implant design
Mette Ørskov Sjøland, 2007. *www.OrthoResearch.dk*

Combination of TGF-β1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo
Anders Lamberg, 2007. *www.OrthoResearch.dk*

Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration
Inger Mechlenburg, 2007. *Acta Orthopaedica (Suppl 329) 2008;79*

Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status
Britta Hørdam, 2008. *www.OrthoResearch.dk*

Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty
Kristian Larsen, 2008. *www.OrthoResearch.dk*

Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants
Mette Krintel Petersen, 2008. *www.OrthoResearch.dk*

CoCrMo alloy, *in vitro* and *in vivo* studies
Stig Storgaard Jakobsen, 2008. *www.OrthoResearch.dk*

Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs
Jørgen Baas, 2008. *Acta Orthopaedica (Suppl 330) 2008;79*

The Influence of Local Bisphosphonate Treatment on Implant Fixation
Thomas Vestergaard Jakobsen, 2008. *www.OrthoResearch.dk*

Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults
Anders Troelsen, 2009. *Acta Orthopaedica (Suppl 332) 2009;80*

Polyethylene Wear Analysis. Experimental and Clinical Studies in Total Hip Arthroplasty.
Maiken Stilling, 2009. *Acta Orthopaedica (Suppl 337) 2009;80*

Step-by-step development of a novel orthopaedic biomaterial: A nanotechnological approach.
Thomas H.L. Jensen, 2009. *www.OrthoResearch.dk*

Osteoclastic bone resorption in chronic osteomyelitis
Kirill Gromov, 2009. *www.OrthoResearch.dk*

Use of medications and the risk of revision after primary total hip arthroplasty
Theis Thillemann, 2009. *www.OrthoResearch.dk*

Different fixation methods in anterior cruciate ligament reconstruction
Ole Gade Sørensen, 2010. *www.OrthoResearch.dk*

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Paper I

Clinical Epidemiology

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ORIGINAL RESEARCH

Chronic infections in hip arthroplasties: comparing risk of reinfection following one-stage and two-stage revision: a systematic review and meta-analysis

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Background: Two-stage revision is regarded by many as the best treatment of chronic infection in hip arthroplasties. Some international reports, however, have advocated one-stage revision. No systematic review or meta-analysis has ever compared the risk of reinfection following one-stage and two-stage revisions for chronic infection in hip arthroplasties.

Methods: The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Relevant studies were identified using PubMed and Embase. We assessed studies that included patients with a chronic infection of a hip arthroplasty treated with either one-stage or two-stage revision and with available data on occurrence of reinfections. We performed a meta-analysis estimating absolute risk of reinfection using a random-effects model.

Results: We identified 36 studies eligible for inclusion. None were randomized controlled trials or comparative studies. The patients in these studies had received either one-stage revision (n = 375) or two-stage revision (n = 929). Reinfection occurred with an estimated absolute risk of 13.1% (95% confidence interval: 10.0%–17.1%) in the one-stage cohort and 10.4% (95% confidence interval: 8.5%–12.7%) in the two-stage cohort. The methodological quality of most included studies was considered low, with insufficient data to evaluate confounding factors.

Conclusions: Our results may indicate three additional reinfections per 100 reimplanted patients when performing a one-stage versus two-stage revision. However, the risk estimates were statistically imprecise and the quality of underlying data low, demonstrating the lack of clear evidence that two-stage revision is superior to one-stage revision among patients with chronically infected hip arthroplasties. This systematic review underscores the need for improvement in reporting and collection of high-quality data and for large comparative prospective studies on this issue.

Keywords: infection, arthroplasty, hip replacement, one-stage, two-stage, reoperation

Introduction

Much has been written in past decades on the treatment of infected hip arthroplasties (HA), as infection constitutes a major cause of revision.[1] The incidence of deep infection following HA has stabilized at less than 1%.[2–5] This severe complication to an otherwise very successful procedure is a large personal and economic burden to the patient and very costly from a societal perspective.[4,6,7] Current treatment options involve a panel of surgical and nonsurgical approaches.[8] Antibiotic suppression therapy is used if the patient is very ill or declines further surgical treatment.[8,9] Debridement and

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antibiotic treatment combined with implant retention is used in early and acute hematogenous infections, but is inferior in chronic infections.[10–12] Direct exchange (one-stage revision) or delayed reimplantations (primarily as two-stage revision) are used in chronic infections. Two-stage revision is currently regarded as the surgical gold standard worldwide.[8,9,13–16] The one-stage approach, pioneered by Buchholz three decades ago, is advocated mainly by European centers.[15,17] One-stage revision has the presumed advantages of a lower personal burden for the patient, a societal economic gain, and an overall better outcome due to fewer surgical procedures and lack of an interim period. The last large review on one-stage revision in the treatment of infected HA was published a decade ago.[18] The authors concluded on the basis of 1299 episodes of infected HA treated by one-stage revision that the indication for one-stage revision was limited due to a high reinfection risk (17% reinfected). The risk estimate was obtained by pooling cases from twelve studies. Cases represented a mixture of acute and chronic infections, and no evaluation of the quality of the research data was performed. Furthermore, no direct comparison was made with other treatment strategies. We found it appropriate to investigate systematically the current evidence for best practice in the treatment of chronic infections in HA, with a focus on retention of a functional hip implant. We performed, to our knowledge, the first systematic review and meta-analysis comparing the risk of reinfection following one-stage and two-stage revision for chronic infection in HA.

Materials and methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[19,20] Our aim was to examine whether one-stage revision is a relevant treatment strategy for chronic infection in HA with respect to the primary-outcome reinfection, as compared to the currently accepted gold standard of two-stage revision. All types of study designs were accepted for inclusion in this review.

Search strategy

Studies were identified by electronic-database searching of PubMed (1966–May 2010), Embase (1980–May 2010), the Cochrane Library, and the World Health Organization platform for international clinical trials registries (http://www.who.int/ictrp). We used a search strategy developed by the first author and a university research librarian, as specified in Table 1.[21]

Table 1 Search strategy

Search performed in the following numerical order (Pubmed/Embase)
#1 Hip arthroplasties
#2 Hip replacement
#3 Hip replacements
#4 Replaced hip
#5 Hip implant
#6 Hip implants
#7 Hip joint replacement
#8 Hip joint replacements
#9 Total hip prosthesis
#10 Hip prostheses
#11 Infection OR infections
#12 One stage OR 1stage
#13 Two stage OR 2 stage
#14 Delayed reimplantation OR stage reimplantation OR staged reimplantation
#15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#16 #12 OR #13 OR #14
#15 #11 AND #15 AND #16

Notes: The search strategy was applied as key concepts. No limits applied. The Cochrane Library was searched using: infection AND hip/infection AND arthroplasty/infection AND hip replacement. The World Health Organization platform for international clinical trials registries (http://www.who.int/ictrp) was searched for ongoing, terminated, or completed trials using: infection AND hip/infection AND arthroplasty/infection AND hip replacement. Keywords used to assess relevancy in the electronic database search: hip, infected, infection, bacteria (or specific species), septic, one-stage, two-stage, direct exchange, exchange, stage, staged, revision, arthroplasty, replacement, prosthesis, treatment, spacer, beads, outcome.

Reference lists of all acquired original and review articles were assessed for relevance and cross-referenced with articles already obtained ("snowballing"). Studies were subjectively assessed by title in the electronic-database search (see criteria used in Table 1), and if deemed relevant, the abstract was retrieved. In cases of possible relevance based on the abstract, the full-length text was obtained. In cases where no abstract was available, the full-length text was obtained.

Eligibility criteria

From the full-length texts obtained, we included all studies that examined patients with an HA and a diagnosed infection of the implant, for whom a defined duration of symptoms or time period from the index implantation to the infection diagnosis was given, who were treated with either one-stage or two-stage revision, and for whom data on occurrence and number of reinfections were available. Selected relevant patient subgroups from broader studies were also able to be included. No restrictions were made according to age, gender, presence of comorbidity, infecting microorganism, primary hip disease, and nature of the index implant or length of patient follow-up. We did not include patients who had

received treatment for a new infection following a prior septic revision, regardless of time interval, or patients who did not complete a reimplantation as part of a planned two-stage revision but were discharged following a Girdlestone/permanent-spacer procedure. We chose to compare only patients with completed one-stage and completed two-stage revision, as we considered this the clinically relevant treatment exposure of interest. Only patients reported in full-length articles were included for analysis. Studies with overlapping patient data were individually assessed and the most appropriate study chosen for inclusion (based on available information and longest follow-up). Eligibility assessment was done by the first author.

Data processing

The following variables were registered: (1) main exposure – patients undergoing one-stage/two-stage revision with completed reimplantation; (2) primary outcome – reinfection; (3) study demographics – first author, publication year, the institution where patients were operated on, the calendar period of inclusion, presence of a study hypothesis, a predefined primary end point, clearly defined in- and exclusion criteria, study design, retrospective or prospective data collection; (4) study population demographics – definition of infection, defined time period between latest surgery to the hip and subsequent infection, duration of infection symptoms prior to revision, the total number of patients eligible for reimplantation,

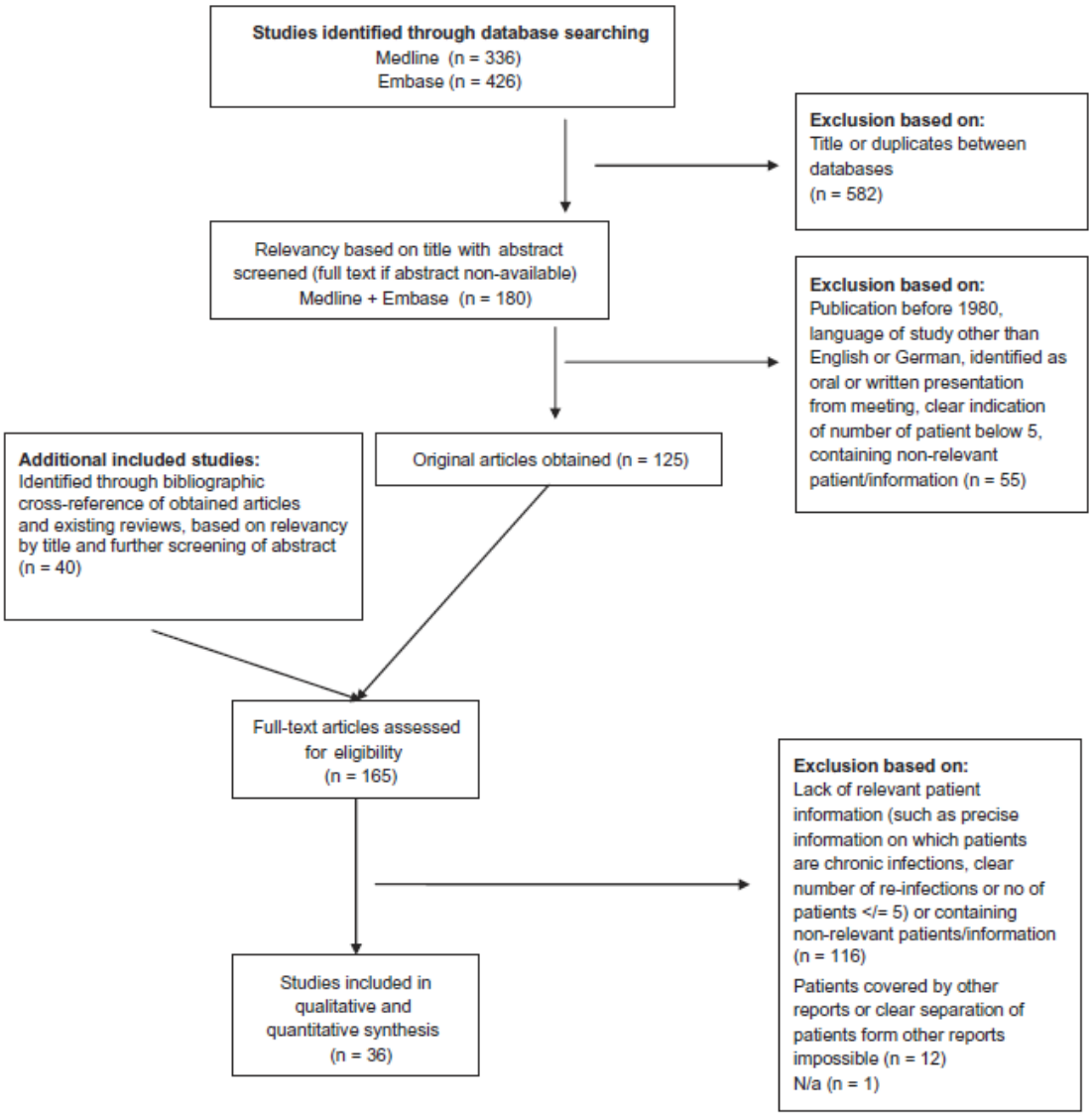

Figure 1 PRISMA flow diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

study size (total number of patients receiving reimplantation), gender, age, patient comorbidity, data on the infected index HA (primary/revision and cemented/cementless), revision for other cause than infection after reimplantation; and (5) perioperative setting – type of implant used at reimplantation (cemented/cementless), follow-up period, microbiological cultures for individual patients, patient assessment score after revision surgery, time interval between stages, the use of spacer/beads or other topical antibiotics, antibiotic treatment regimen. Data were extracted independently by the first and second authors. Disagreement was resolved by consensus.

Summary measures

We performed meta-analysis estimating the absolute risk (hereafter referred to simply as "risk") with 95% confidence intervals of the primary outcome with a random-effects model. The analysis was performed using extracted patient data from the individual studies. Subgroup analysis on the risk of reinfection was done for main exposure and further stratified by type of implant used at reimplantation. We performed meta-regression for all studies and stratified by main exposure regarding study size and publication year on risk of reinfection. We performed sensitivity analysis by means of "one-study removed" to detect outliers and evaluate single-study impact on the derived estimates. By a priori acknowledgment of significant inconsistency among studies and by taking this into account using a random-effects model, we did not further quantify existing heterogeneity.[22] All data management was done using Comprehensive Meta-Analysis (v2.0; BioStat, Englewood, NJ). In the case of zero-outcome events, this program adds 0.5 to the value of both outcome events and sample size and uses these modified values for all future calculations (eg, no events in 20 patients: 0.5/20.5 = risk of 0.024). Forest plots were produced to qualitatively evaluate study heterogeneity and graphically support risk estimates. Funnel plots were used to graphically assess the possibility of publication bias. Such bias was believed a priori to exist for small studies with poor results.[23] Assessment of methodological or clinical limitations for the included studies was done with a focus on key study features, these being: (1) patient sample – well-defined inclusion criteria, mode of data collection, defined patient demographics; (2) follow-up – sufficiently defined as more than 2 years; (3) outcome – adequate description regarding infection diagnosis; and (4) treatment – perioperative treatment regimens.[20,21]

Results

Study selection

A total of 165 full-length articles were assessed for eligibility (Figure 1). Of these, 36 studies were considered eligible for

Table 2 Characteristics of studies with patients in the one-stage revision cohort

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Gender, % male	Age, years (range)	Time with infection/ infected prosthesis
Yoo et al[47]	Cementless	12	1991–2005	67	50 (29–72)	3.6 years (1.2–9.8)
Lai et al[48]	Cementless	7	1991–1993	71	62 (52–68)	"Late or delayed"
Rudelli et al[49]	Cementless	6	1989–1994	50	60 (39–71)	Minimum 4 months
Mulcahy et al[50]	Cemented	15	n/a	87	64 (49–82)	2.2 years (6 months–16 years)
Callaghan et al[51]	Cemented	24	1977–1983	50	65 (37–86)	4.9 years (1–11)
Hope et al[52]	Cemented	72	1976–1987	44	64 (30–85)	n/a (>3 weeks after pre-op aspiration)
Ure et al[53]	Cemented	20	1979–1990	80	61 (32–85)	53 months (6.6–148)
Raut et al[54]	Cemented	183	1979–1990	52	65 (17–84)	n/a (referalls)
Drancourt et al[55]	Cemented	10	1987–1991	n/a	n/a	32.6 months (1–130)
Rudelli et al[49]	Cemented	26	1991–2000	38	62 (37–83)	minimum 4 months

inclusion in the review. Of the 36 included studies, 31 (86%) were identified by the electronic-database search. The World Health Organization search revealed one relevant ongoing trial (Cementless One-Stage Revision of the Chronic Infected Hip Arthroplasty; NCT01015365). No relevant completed or terminated trials were registered. The search of the Cochrane Library revealed no further relevant studies. The cross-referenced reviews were acquired as part of background research.[8,9,14,15,18,24–46]

Description of included studies

Study characteristics are summarized in Tables 2 and 3. The patients in the 36 included studies were divided into two cohorts of distinctly separate revision strategies: a one-stage-revision cohort (Table 2) comprising relevant patients from ten studies (n = 375 [cementless reimplantation, n = 25 patients;[47–49] cemented reimplantation, n = 350 patients[49–55]]) and a two-stage-revision cohort (Table 3) comprising relevant patients from 28 studies (n = 929 [cementless reimplantation, n = 189 patients;[48,56–62] cemented reimplantation, n = 177 patients;[63–69] no specific information on type of reimplantation at patient level, n = 563 patients[11,13,16,70–78]]). Gender and age did not differ between the cohorts based on the available data. In the one-stage cohort, 195 of 365 (53.4%) patients were male, compared to 400 of 699 (57.2%) patients in the two-stage cohort, although 230 of 929 (24.8%) patients in the two-stage cohort had no data on gender, compared to ten of 375 patients in the one-stage cohort. The reported average age in the one-stage cohort was 61.4 years, compared to 63.1 years in the two-stage cohort. Data on comorbidity on a patient level or for the study cohort as a whole were only available in 14 studies (in only one of ten studies with patients in the one-stage cohort, compared to 14 of 28 studies with patients in the two-stage cohort). Thirteen of the 36 studies originated from North America, eleven from Europe, nine from Asia/Australia and three from South America. In the one-stage cohort, 280 of 375 (75.0%) patients originated from European studies, as did 261 of 929 (28.1%) in the two-stage cohort. In contrast, only 44 of 375 (11.7%) patients in the one-stage cohort and 445 of 929 (48.0%) patients in the two-stage cohort originated from North American studies. The one-stage cohort studies tended to be older: six of ten studies were published in the period 1990–1999 and three of ten studies were published after 1999, whereas in the two-stage cohort seven of 28 studies were published in the period 1990–1999 and 20 of 28 studies after 1999. Regarding the methodology of the included studies, we found no comparative studies that compared patients exposed to one-stage revision with a concurrent or historical control group of patients with two-stage

Antibiotic treatment regime (study level)	Non-septic revisions after reimplantation, n (%)	Follow-up, month (range)	Definition of infection (study level)
iv or iv/po combined for 3–24 weeks	1 (8)	86.4 (39.6–135.6)	Chronic hip pain + purulent fluid/pus on op + elevated crp or SR (a positive culture to be included in study)
iv 2–6 weeks then po min 2 months	n/a	42 (33–54)	Positive culture
iv min 4 weeks then po, total 6 months	0	138.7 (101–173)	A positive culture from min 6 samples (2 pt only fistula, 1 pt. Only pos culture from pre-op aspiration)
iv 3 weeks	0	48 (24–84)	Positive culture
iv 10 days then po 3–6 months	1 (4)	109.2 (12–168)	Positive culture + purulence/inflammation during opertion
n/a	2 (3)	45 (5–121)	"Clinical, hematological and radiological criteria" (in study only CNS proven infections)
iv 2–18 weeks then po 3–6 months	2 (10)	123.6 (66–205.2)	A positive culture + >5 polymorph leukocytes per field
iv 1–4 weeks then po 6 weeks–3 months	4 (2)	83 (24–164)	Pyogenic granulation tissue or pus or sinus + radiologic evidence + bacteriology
po 5 months before and 1 month after revision	n/a	27.6 (9–61)	Fistula or pain and elevated crp and SR > 50 or radiological loosening and elevated crp and SR > 50 AND 2 positive cultures
iv min 4 weeks then po, total 6 months	0	84.1 (42–175)	A positive cultures from min 6 samples (2 pt only fistula, 1 pt. Only pos culture from pre-op aspiration)

Abbreviations: n/a, not available; iv, intraveneous; po, per os; crp, c-reactive protein; SR, sedimentation rate.

Table 3 Characteristics of studies with patients in the two-stage-revision cohort

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Time with infection/ infected prosthesis	Gender, % male	Age, years (range)	Interval between first revison and reimplantation (range)
Lai et al[48]	Cementless	19	1991–1993	"late or delayed"	89	49 (29–67)	32,5 weeks (8–66)
Buttaro et al[56]	Cementless	29	1997–2000	11.7 months (3–48)	40	59 (32–78)	14.7 weeks (5–96)
Fehring et al[57]	Cementless	22	n/a	"Chronic infections"	n/a	n/a	4,7 months
Fink et al[58]	Cementless	36	2002–2006	4,4 years (±4 years)	44	69 (sd ±10)	6 weeks for all
Hofmann et al[59]	Cementless	27	1991–2001	63 months (2–413)	56	64 (38–87)	14 weeks (3–49)
Koo et al[60]	Cementless	12	1993–1997	8.25 months (2–36)	75	56 (37–73)	6 (6–8)
Yamamoto et al[61]	Cementless	10	1998–2002	48 days (32–73)	50	63 (44–76)	125 days (85–245)
Nestor et al[62]	Cementless	34	1984–1989	24 months, (1–108)	n/a	61 (26–70)	7 months (3–19)
McDonald et al[63]	Cemented	81	1969–1985	2,5 years (31 days–14,8 years)	53	60 (33–80)	1.5 years (6 days–6.2 years)
Cordero-Ampuero et al[64]	Cemented	20	1997–2007	>3 months since index surgery	40	67 (46–80)	9,1 months (3–23)
Evans[65]	Cemented	11	1995–2002	MSIS stage III	55	70 (43–90)	98 days (44–192)
Magnan et al[66]	Cemented	8	1996–1999	2–168 months	75	71 (58–83)	5 months (3–9)
Dairaku et al[67]	Cemented	7	n/a	50 months (2–103) (duration of infection before revision 1–12 months)	29	65 (55–81)	15 weeks (12–22)
Nusem and Morgan[68]	Cemented	18	1990–1999	6 years (2–10)	n/a	66 (45–86)	5 months (1–8)
Lieberman et al[69]	Cemented	32	1985–1988	41 months (1–186)	n/a	67 (32–89)	62 days (20 days–32 months)
Sanchez-Sotelo et al[70]	Unknown	168	1988–1998	5,1 year (4 months–20 years)	65	67 (32–89)	9,4 months (3–18)
Stockley et al[71]	Unknown	114	1991–2004	"Chronic infections"	55	64 (28–83)	6,4 months (2–22)
Hanssen and Osmon[13]	Unknown	17	1996–1997	26 months (1.4–28) (duration of infection MCPherson stage III)	47	64 (31–82)	159 days (90–780)

Spacer (with antibiotics)/beads/none	Antibiotic treatment regimen (study level)	Non-septic revisions after reimplantation, n (%)	Follow-up, month (range)	Definition of infection (study level)
Beads only 19 patients	iv 2–6 weeks then po min 2 months	n/a	38 (25–51)	Positive culture
None	iv 5–8 weeks then po 4–16 weeks	1 (3)	32.4 (24–60)	A positive culture from five samples
Beads only 16 patients	iv 6 weeks	1 (5)	37.5 (24–98)	A positive culture or positive histology for infection
Spacer (w)	iv 2 weeks then po 4 weeks	0	35 (24–60)	Pre-op hip aspiration and observation of the same microorganism in at least two of five cultures and observation of a microorganism in at least one sample and at least five neutrophilic polymorphonuclear leukocytes per high-power field (×400) in the associated histologic preparation
Spacer (w)	iv 6–8 weeks then for 17 pt po for 6 weeks	n/a	76 (28–148)	A positive culture or clinical history + elevated CBS, CRP, ESR + inflammation on frozen section
	iv 6 weeks	0	45 (24–66)	Positive culture or pus
Spacer (w)	iv 2–12 months	n/a	42.6 (5–62)	"Infection"
None	iv 28 days (9–42) then po 14 days (0–40)	2 (6)	47 (24–72)	Combination of pain, draining sinus, fever, haematolgical markers, scintigraphic scans, pre-op aspiration with positive cultures OR positive intraoperative cultures
None	iv 26 days (4–59) (two pt received oral instead). No antibiotics in cement	7 (9)	66 (24–163, 2)	Histological evidence of infection and positive culture or gross purulence
None	iv < 5 days then po 6 months	n/a	55,2 (12–132)	3 or more positive cultures
Spacer (w)	iv 6 weeks	0	24 (24)	"Infection" (10 culture positive, 1 culture negative)
Spacer (w)	n/a	0	36 (24–48)	"Infection" (4 culture positive, 4 culture negative)
Spacer (w)	n/a	1 (14)	18 (6–68)	Culture postitive (1 pt elevated crp + osteolysis)
Spacer (w)	iv 3–4 weeks then po 1–31 weeks	2 (11)	108 (60–168)	"Infection" (all patients seemingly culture positive)
Beads 4 patients	iv 41 days (20–49). Antibiotics in cement in only 17 pt	0	40 (24–75)	Culture positive
Spacer (w) 31 patients	iv 6 weeks (3–18)	34 (20)	24 (n/a–192)	Two or more positive cultures (n = 146) OR culture from pre-op aspiration with preoperative signs of infection: "frank pus", histopathologic exam, sinus
Beads	iv only 1. Postoperative day	n/a	74 (2–175)	Culture positive
None	n/a	n/a	n/a	Culture positive

(Continued)

Table 3 (*Continued*)

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Time with infection/ infected prosthesis	Gender, % male	Age, years (range)	Interval between first revison and reimplantation (range)
Incavo et al[72]	Unknown	11	n/a	47 months (3–240)	n/a	n/a	n/a (6–24weeks)
Takigami et al[78]	Unknown	8	1999–2006	18,6 months (1–56)	75	65 (49–79)	16,8 weeks (12–27)
Lim et al[73]	Unknown	34	1995–2006	41 months (2–144)	n/a	59 (35–79)	20 weeks (6–88)
Tsukayama et al[11]	Unknown	34	1980–1991	">one month after index op and had an insidious course"	n/a	n/a	110 days (34–720)
Wang et al[74]	Unknown	22	1988–1993	4,6 years (4 months – 11 years)	82	48 (28–75)	6,6 months (1,5–24)
Whittaker et al[75]	Unknown	43	1998–2003	12 months (3–36)	49	69 (33–90)	21 weeks (8 weeks–23 months)
Cabrita et al[16]	Unknown	55	1996–2003	>4 weeks	n/a	n/a	n/a (60–610 days)
Isiklar et al[79]	Unknown	9	1996–1998	28 months (3–96) (duration of infection > 6 weeks)	33	63 (38–78)	7 weeks (3–14)
Scharfenberger et al[80]	Unknown	8	1998–2003	>2 months	n/a	n/a	n/a
Walter et al[77]	Unknown	40	2001–2005	> 4 weeks	55	66 (48–86)	n/a

revision, or vice versa. One study was a randomized trial of spacer versus no-spacer treatment in patients who had all had two-stage revision.[16] Another study was a case-control study in patients with performed two-stage revision had become infected with resistant versus nonresistant microorganisms.[73] One study used cohort-outcome analysis to examine predictors of reinfection.[63] The remaining 33 of the 36 (92%) studies were purely descriptive case series of infected HA patients treated with one-stage or two-stage revision, reporting patient characteristics and frequencies of different outcomes, including reinfection. Twenty-eight of 36 (78%) studies used retrospective data collection. Only two studies described a priori defined primary end points. Three studies stated a study hypothesis, and 14 studies provided some degree of background information on in- and exclusion criteria for enrollment in the study. Eighteen studies did not report on the status of the infected index HA (being a primary/revision or cemented/cementless prosthesis). Fifteen studies evaluated the revision procedure by means of the Harris hip score.[11,16,47,48,50,57–59,61,64,68–70,77,79] Twelve studies did not use a standardized scoring system in evaluating patients postoperatively.[13,51,52,55,60,63,65,66,71–73,80] Four studies used the Merle d'Aubigné–Postel score.[49,54,56,75] The remaining five studies used other scoring systems.[53,62,67,74,78] Methodological characteristics of the included studies are shown in Table 4. In conclusion, methodological quality was considered low for most included studies, and we found no comparative studies examining one-stage versus two-stage revision.

Meta-analysis

We pooled data from 36 studies with a total of 1304 patients having a completed one-stage or two-stage revision and 126 registered reinfections following the reimplantation. Sensitivity analysis did not detect outliers, nor did it indicate that any estimate was heavily determined by a particular study. We found that reinfections for all studies occurred with an estimated risk of 11.3% (95% confidence interval [CI]: 9.6%–13.2%) (Figure 2). Reinfection occurred with an estimated risk of 13.1% (95% CI: 10.0%–17.1%) in

Spacer (with antibiotics)/beads/none	Antibiotic treatment regimen (study level)	Non-septic revisions after reimplation, n (%)	Follow-up, month (range)	Definition of infection (study level)
Spacer (w)	iv 4–6 weeks (then "some" patients po)	n/a	n/a	Culture positive
Ceramics blocks (w)	iv 4.2 weeks (2–8)	0	49 (24–81)	"… based on clinical, radiological and histological evidence …" – 6 pt culture positive
Spacer (w) or beads	iv 9.6 weeks (4–24)	2 (6)	52,8 (24–120)	2 or more positive culture OR histopathological exam OR sinus
Beads (w)	iv 6 weeks	n/a	50,4 (15,6–132)	Min 2 of 5 positive cultures OR pus preoperatively
Beads 13 patients	iv 16 days (7–42)	3 (9)	48 (24–84)	Preoperative pus or histopathological exam (all patients culture positive)
Spacer (w)	iv 2 weeks	0	49 (25–83)	2 or more positive cultures or histopathological exam
Spacer (w) 33 patients	iv 3 weeks then po 6 months	6 (11)	48 (24–102)	Culture positive
Spacer (w)	iv 3–14 weeks then po 12–24 weeks	0	24 (160–36)	S. Epidermidis proven infection
Spacer (w)	iv 6 weeks	1 (13)	n/a (24–n/a)	Culture positive
Beads or spacer (w)	Min 6 weeks, of iv + po	4 (10)	7 (3–48)	Culture positive

Abbreviations: n/a, not available; iv, intraveneous; po, per os; crp, c-reactive protein; SR, sedimentation rate.

the one-stage cohort and with an estimated risk of 10.4% (95% CI: 8.5%–12.7%) in the two-stage cohort (Figure 3). In the two-stage cohort, cementless reimplantation yielded a reinfection risk of 8.6% (95% CI: 4.9%–14.7%), and cemented reimplantation a reinfection risk of 12.3% (95% CI: 8.0%–18.4%) (Figure 4). In the one-stage cohort, only very limited data were available for cementless reimplantation (a total of just 25 cases). Meta-regression showed no correlation between study size and risk of reinfection pooling all studies ($\beta = 0.002$, $P = 0.172$) or within the two-stage cohort ($\beta = -0.002$, $P = 0.486$). However, within the one-stage cohort, a larger study size correlated with a higher risk of reinfection ($\beta = 0.005$, $P = 0.048$). Further exploration showed that the single study by Raut et al[54] had a considerable role in this correlation, with a relative weight of 62% in the one-stage group; however, this was not detected as statistically significant by sensitivity analysis. Meta-regression indicated that a more recent publication pooling all studies correlated with a lower risk of reinfection ($\beta = -0.029$, $P = 0.020$), but no correlation could be identified when stratified (one-stage cohort: $\beta = -0.032$, $P = 0.346$; two-stage cohort: $\beta = -0.026$, $P = 0.098$). Graphical evaluation of funnel plots confirmed the likely presence of missing smaller studies with higher reinfection risk.

Discussion

Summary of evidence

The results of this meta-analysis suggest the presence of nearly three additional reinfections per 100 reimplanted patients when performing a one-stage revision compared to a two-stage revision strategy for treatment of chronic infection in HA. However, we believe it is difficult to draw any conclusions on the superiority of either revision strategy from the available data. Even with the reasonably large number of studies, the pooled reinfection-risk estimates were statistically imprecise, with overlapping confidence intervals. Furthermore, one must consider that these risk estimates are based purely on data from case series with limited information on potential confounding factors. No single study has directly compared the two revision strategies. Also, the different

Table 4 Methodological characteristics of included studies

Authors	Study design	Comparing cohorts of 1- vs 2-stage revision	Data colletion	In-/exclusion clearly defined	Co-morbidity defined or includeded patients (study or patient level)	Follow-up more than 2 years for all patients	Patient level information regarding microbial diagNosis and antibiotic treatment regimen	Number of urgeons performing there visions	Information on nature of infected index prosthesis
Yoo et al[47]	Cohort	No	Retrospective	Yes	No	Yes	No	Yes	Yes
Lai et al[48]	Cohort	No	Retrospective	No	Yes	Yes	No	Yes	Yes
Rudelli et al[49]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Mulcahy et al[50]	Cohort	No	Retrospective	No	No	Yes	No	Yes	No
Callaghan et al[51]	Cohort	No	Retrospective	Yes	No	No	No	No	Yes
Hope et al[52]	Cohort	No	Retrospective	Yes	No	No	No	Yes	Yes
Ure et al[53]	Cohort	No	Prospective	No	No	Yes	Yes	No	No
Raut et al[54]	Cohort	No	Prospective	No	No	Yes	No	Yes	Yes
Drancourt et al[55]	Cohort	No	Prospective	Yes	No	Not	Yes	No	No
Buttaro et al[56]	Cohort	No	Retrospective	Yes	No	Yes	No	No	Yes
Fehring et al[57]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Fink et al[58]	Cohort	No	Prospective	Yes	Yes	Yes	No	No	Yes
Hofmann et al[59]	Cohort	No	Retrospective	No	No	Yes	No	Yes	Yes
Koo et al[60]	Cohort	No	Retrospective	No	No	Yes	Yes	No	Yes
Yamamoto et al[61]	Cohort	No	Retrospective	No	Yes	No	No	No	Yes
Nestor et al[62]	Cohort	No	Retrospective	No	No	Yes	Yes	Yes	Yes
McDonald et al[63]	Cohort	No	Retrospective	No	No	Yes	No	No	Yes
Cordero-Ampuero et al[64]	Cohort	No	Prospective	Yes	No	No	Yes	No	No
Evans[65]	Cohort	No	Retrospective	No	Yes	Yes	Yes	No	No
Magnan et al[66]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Dairaku et al[67]	Cohort	No	Retrospective	No	No	No	Yes	No	Yes
Nusem and Morgan[68]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Lieberman et al[69]	Cohort	No	Retrospective	Yes	No	Yes	No	No	No
Sanchez-Sotelo et al[70]	Cohort	No	Retrospective	Yes	Yes	Yes	No	No	Yes
Stockly et al[71]	Cohort	No	Prospective	No	No	No	No	Yes	No
Hanssen and Osmon[13]	Cohort	No	Retrospective	No	Yes	No	No	Yes	Yes
Incavo et al[72]	Cohort	No	Retrospective	No	Yes	No	No	No	Yes
Takigami et al[78]	Cohort	No	Retrospective	No	No	Yes	Yes	No	No
Lim et al[73]	case-control (-on sensitivity pattern)	No	Retrospective	Yes	Yes	Yes	No	Yes	No
Tsukayama et al[11]	Cohort	No	Retrospective	No	No	No	No	No	Yes
Wang and Chen[74]	Cohort	No	Retrospective	No	Yes	Yes	No	No	Yes
Whittaker et al[75]	Cohort	No	Prospective	Yes	Yes	Yes	No	No	No

Cabrita et al[16]	RCT (spacer vs no spacer)	No	Prospective	Yes	Yes	Yes	No	No	No	No
Isiklar et al[79]	Cohort	No	Prospective	Yes	Yes	No	Yes	No	No	No
Scharfenberger et al[80]	Cohort	No	Retrospective	Yes	Yes	Yes	No	No	No	No
Walter et al[77]	Cohort	No	Prospective	No	Yes	No	No	No	No	No

clinical settings and patients underlying the two revision strategies must be taken into account. Nevertheless, we have demonstrated the lack of clear evidence proving one-stage revision to be a less effective treatment strategy for chronic infections in HA, as has been previously claimed.[18]

Strengths and limitations

The data presented in this review are the best available at present to clinicians worldwide, and have so far been used to advocate the different treatment strategies offered.[9,18] We quantified these data for the first time in a systematic review and meta-analysis. Yet it became apparent that neither controlled clinical trials nor observational studies have directly compared one-stage and two-stage revision for treatment of chronic infections in HA. The estimates obtained in this review are obtained from a wide diversity of patients, the majority of studies were small and based on retrospective data collection, and results from the two cohorts should be compared with great caution. Due to the unavailability of confounding factors in many of the studies, we chose simply to estimate pooled absolute risks of reinfection in the two cohorts, rather than a risk-ratio estimate in a direct comparison, as we had no way to control for potentially skewed distribution of covariates. Ignoring this would in our opinion compromise the entire study. We thus believe the reported absolute estimate gives a fair opportunity for better understanding the conclusions drawn from this review.[81] Yet several aspects must be emphasized.

Terminology

Infection in HA is by far the most difficult area to define, as this is often covered by a multitude of overlapping symptoms and clinical findings, which added together strongly indicate a septic complication. Even the gold standard in diagnosing infection – perioperative cultures – is not absolute. Culture-negative patients may still be infected, and single- or even double-positive culture may represent contamination.[82,83] Several different definitions of infection have been used in the included studies (Tables 2 and 3). We chose a pragmatic approach for our review, and defined the presence of infection as defined by the authors of the individual study. However, as the definition of infection and reinfection in the 36 included studies varied considerably, ranging from "infection"/clinical features of infection to obtainment of positive bacterial cultures, the risk of misclassification is inherent. For example, patients with aseptic loosening may have been misclassified as reinfected, whereas patients with true infection who did not undergo reoperation after revision may have been missed.

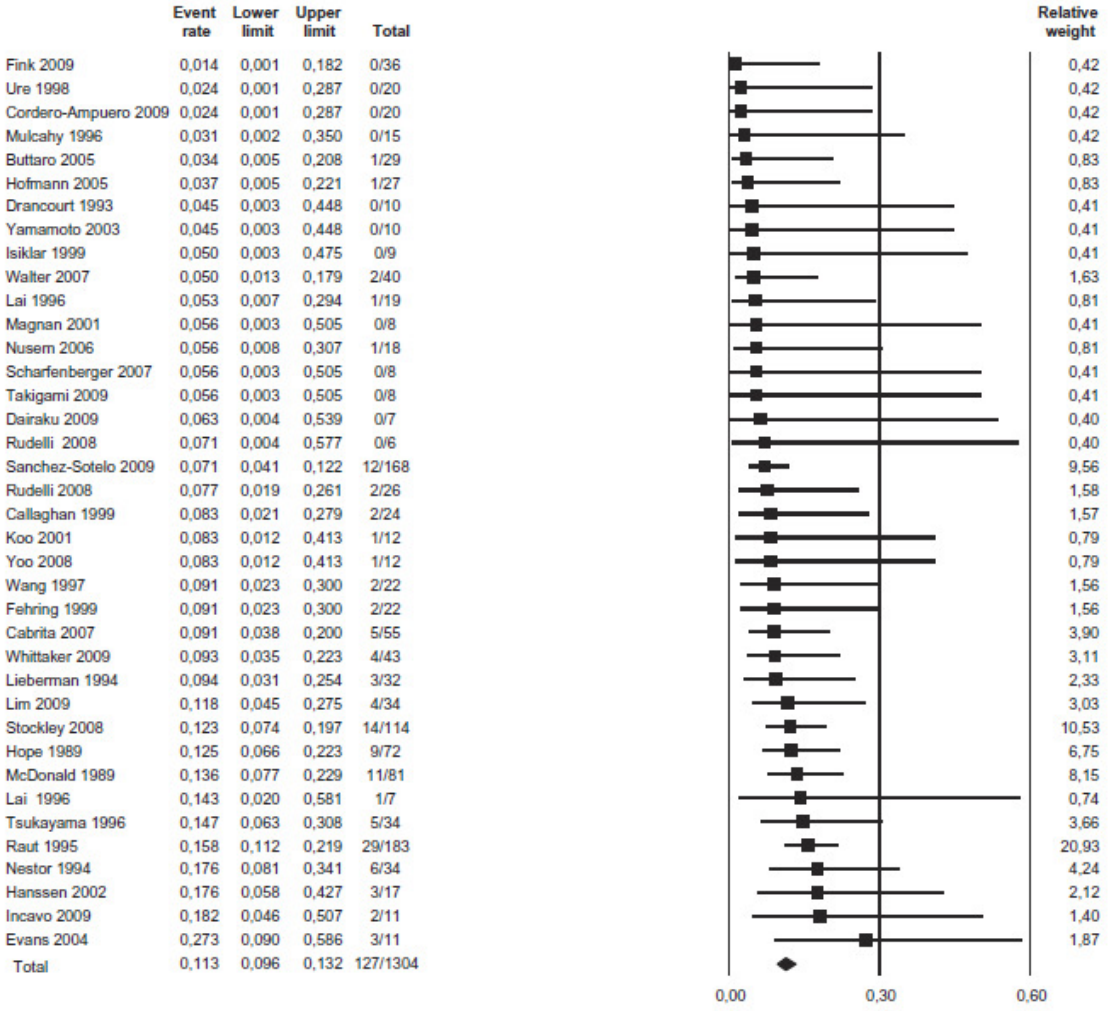

Figure 2 Forest plot illustrating absolute risk of reinfection in ascending order with relative weight of individual studies.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.

Many definitions of "chronic infection" exist.[8,11,13,29,45,84–86,87] A priori, we aimed to define chronic infections according to McPherson, as infections with a duration of symptoms above 4 weeks, regardless of origin.[88] This has also been advocated by others as the best definition at present and has been used recently, in studies of arthroplasty infections and HA studies in particular, by multiple international orthopaedic centers.[13,26,77,89–91] However, during study selection, it became apparent that the definition by McPherson[88] was very difficult to apply to the existing literature, as many studies reported only the interval from last operation to subsequent revision or from last operation to diagnosis of infection. Subsequently, we also chose to include studies that defined chronic infections as more than 1 month since last surgery, regardless of symptom duration, and by authors stating an infection as chronic (Tables 2 and 3).[11] If no data were available regarding these time limits, the study or patients were not included in our review. Thus we may have included patients with acute hematogenous infections, and we may have excluded potentially eligible patients from our analysis. A very strict definition of chronic infection at patient level is thus an element not taken into account in this analysis, as these data were not available to the authors.

Risk-factor assessment

Many apparent risk factors have been suggested to predict worse outcomes when treating infected hip arthroplasties, but few have been validated and the quality of evidence is poor.[5] Concerning the present study, 60% of studies in the one-stage cohort were published in the period 1990–1999, while 71% of studies in the two-stage cohort were published after 1999. A generally decreased risk of reinfection over time may have

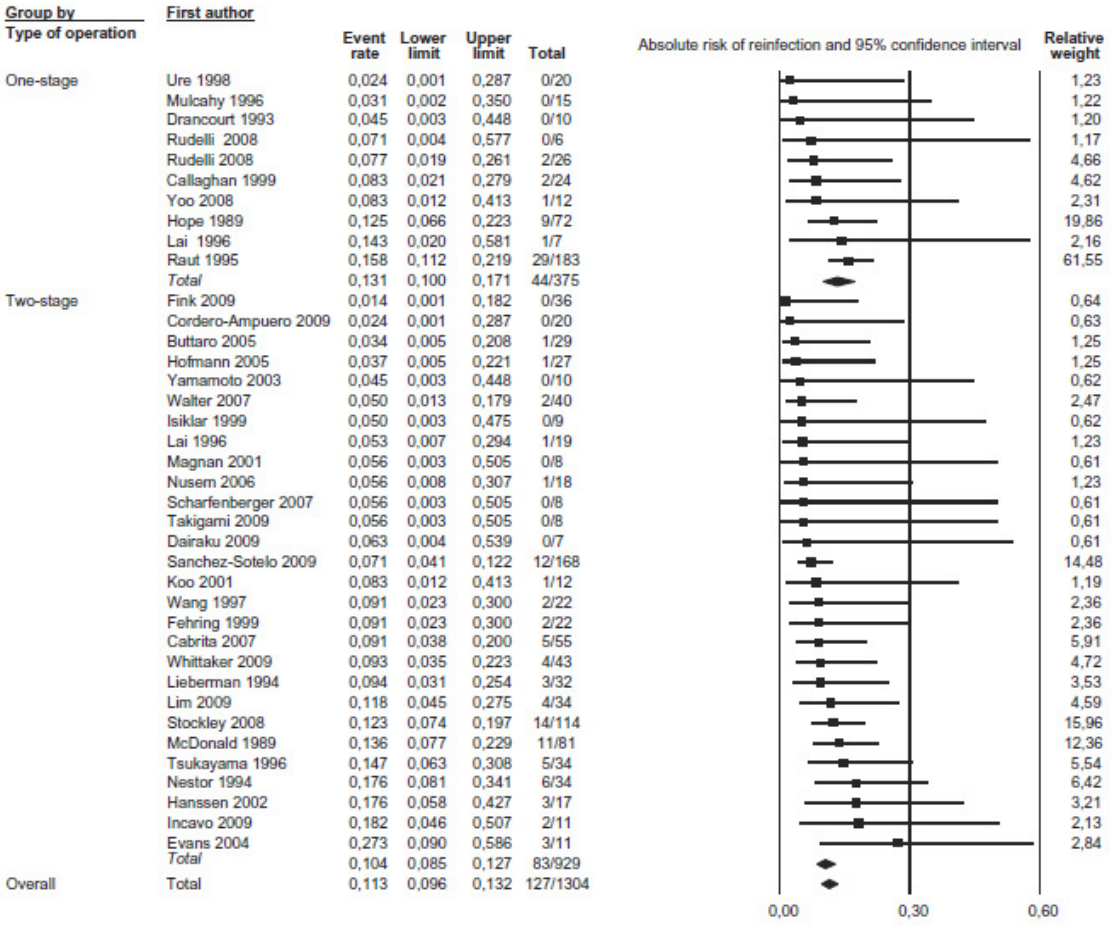

Figure 3 Forest plot illustrating stratified analysis by type of revision performed with relative weight of individual studies.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.

led to an overestimation of the reinfection risk associated with one-stage procedures conducted many years ago. As our understanding of the importance of many different treatment aspects increases over time, so may our overall results improve, regardless of the chosen surgical strategy. The articles from which data are analyzed span more than two decades; surgical techniques and materials used have evolved, as well as general knowledge on infections and patient care. Undoubtedly, better knowledge of optimal antibiotic therapy in prophylactic and active treatment, eg, the use of antibiotic-enriched cement and differences in local resistance patterns, but also the emergence of multiresistant organisms, could have influenced the reinfection risk over time. Improved understanding of biofilm-producing microorganisms is

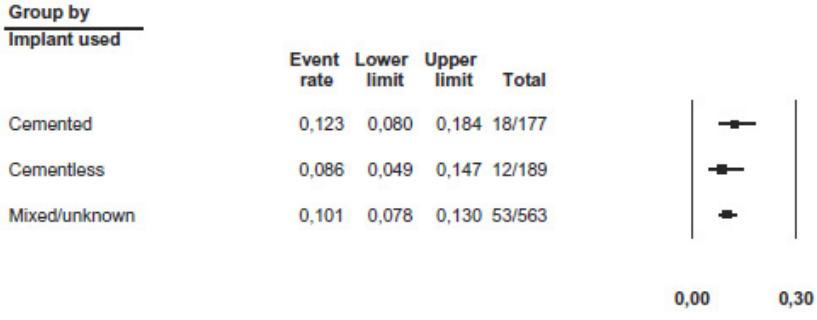

Figure 4 Forest plot illustrating two-stage revision stratified by implant used in reimplantation.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.
Abbreviation: CI, confidence interval.

essential in today's aggressive debridement approach, recognizing the need for absolute removal of dead matter and foreign materials. Our review does not take these important developments over time into account, as good data on these risk factors do not exist in the present studies. Comorbidity, high American Society of Anesthesiologists score, long duration of the surgical procedure, and low hospital and surgeon volume have been suggested as important risk factors for reinfection.[5] In contrast, gender or increased age apparently do not constitute important risk factors, but data quality is poor and conflicting evidence exists.[5,92] Age and gender were also quite evenly distributed in the one-stage and two-stage cohorts in this review. Explicit data on comorbidity at a patient level or even just study level is absent from most studies, as only 14 of 36 studies reported this data. In our opinion, the apparent large difference in reported patient comorbidity (10% among one-stage studies versus 50% among two-stage studies) is most likely due to underreporting, not ignoring that a possible genuine lower comorbidity in the one-stage cohort on the other hand may have led to an underestimation of the reinfection risk associated with this procedure. Furthermore, certain types of medication may directly constitute risk factors, including treatment with bisphosphonates.[93] However, information on medical treatment of the included study populations is not available. The chosen antibiotic treatment strategy is an area of specific interest regarding reinfection, as the surgical procedure by itself does not resolve the infection. Furthermore, the nature of the infecting microorganism may be a key element regarding outcome. Thus, Gram-negative organisms, multiresistant organisms, and polymicrobial infections have been proposed to predict worse outcomes. As shown in Tables 3 and 4, this information is not readily available in the existing studies to a degree at which we could adjust for any differences in these and other risk factors in our meta-analysis.

Potential bias

Whether to choose a specific surgical intervention in a non-research, everyday clinical practice environment is determined by many factors. This raises the concern of whether the selection of patients in the individual 36 studies is alike, with consequences for the comparability of the two cohorts in this review. As noted above, a potentially skewed distribution of unreported or unknown confounders may exist. Confounding by indication (surgical bias) could potentially influence the results obtained in this analysis, as surgeons may choose less severely ill patients (eg, with known nonresistant microorganisms) for one-stage revision. By the very nature of two-stage surgery, the surgeon is able to evaluate the progress before reimplantation, this being one of the clinical strengths of this approach compared with one-stage revision. The exclusion in our meta-analysis of patients for whom the second stage was not completed may favor the two-stage approach, since the patients who did not undergo the second stage may constitute a group with poor outcomes. Finally, by limiting our search to English- and German-language studies from only two electronic databases, we may have overlooked studies published in nonindexed journals, or data presented at national or international conferences, which most likely would include more unfavorable results.

Implications for future research

We believe that complications and outcomes (including validated patient-related outcomes measures) of the different revision strategies need more research attention. Recently, the proportion of complications with interim-spacer application has been reported as high as 60%, and fatal complications have also been reported.[16,91] Appropriate patient selection seems to be a crucial aspect of success.[15,40,94] Given the complexity and relative scarcity of patients with chronically infected HA, randomized clinical trials may prove difficult to perform. The estimates obtained in our analysis suggest that a sample size of more than 3500 infected patients would be needed to investigate superiority of two-stage versus one-stage revision regarding reinfection with statistical precision. Meanwhile, we recommend adoption of standardized reporting of essential data among patients treated for chronically infected HA to ensure the future possibility of performing improved collaborative meta-analysis.[21] We thus recommend that future publications on this matter include relevant individual patient information, making it possible to pool data on a patient level, including detailed data on potential risk factors, duration since last surgical procedure, the duration of symptoms, clear information regarding diagnosis of infection, and grade according to the modified McPherson staging system.[13]

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Paper II

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ORIGINAL ARTICLE

Do hip prosthesis related infection codes in administrative discharge registers correctly classify periprosthetic hip joint infection?

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ABSTRACT

Purpose: Administrative discharge registers could be a valuable and easily accessible single-sources for research data on periprosthetic hip joint infection. The aim of this study was to estimate the positive predictive value of the International Classification of Disease 10th revision (ICD-10) periprosthetic hip joint infection diagnosis code in the Danish National Patient Register.

Methods: Patients were identified with an ICD-10 discharge diagnosis code of T84.5 ("Infection and inflammatory reaction due to internal joint prosthesis") in association with hip-joint associated surgical procedure codes in The Danish National Patient Register. Medical records of the identified patients (n = 283) were verified for the existence of a periprosthetic hip joint infection. Positive predictive values with 95% confidence intervals (95% CI) were calculated.

Results: A T84.5 diagnosis code irrespective of the associated surgical procedure code had a positive predictive value of 85% (95% CI: 80-89). Stratified to T84.5 in combination with an infection-specific surgical procedure code the positive predictive value increased to 86% (95% CI: 80-91), and in combination with a noninfection-specific surgical procedure code decreased to 82% (95% CI: 72-89).

Conclusions: Misclassification must be expected and taken into consideration when using administrative discharge registers for epidemiological research on periprosthetic hip joint infection. We believe that the periprosthetic hip joint infection diagnosis code can be of use in future single-source register based studies, but preferably should be used in combination with alternate data sources to ensure higher validity.

Keywords: Hip Replacement Arthroplasty, Prosthesis related infection, Registries, Epidemiology, Diagnosis, Predictive value

Introduction

Periprosthetic joint infection (PJI) is a relatively uncommon complication following hip joint replacements (HJR) (1). Based on administrative discharge registers, periprosthetic joint infection (PJI) in hip joint replacements (HJR) occur in less than 1 in 2000 primary total hip replacements within 90-day postoperatively (2). Whereas the cumulative 10-year rate after primary total hip replacements is estimated at 2.22% (3). Clinical studies on PJI with sufficient long-term follow-up, especially concerning prognosis and risk factor assessment, may prove extremely difficult to perform (4). Thus, there is an apparent need for easily accessible research data for surveillance on PJI. This need could be met by single-source data from administrative discharge registers. Administrative discharge registers, such as the Medicare 5% sample claims database (5) or the National Hospital Discharge Survey (6), could be valuable and cost-effective methods of acquiring data, both for healthcare quality monitoring and for epidemiological research. Studies originating from administrative discharge registers have been published numerously regarding outcome following HJR (1, 3, 6-8). Data from administrative discharge registers are readily available to researchers and with a potential for long-term follow-up. Data is prospectively collected and independently of specific research questions and may include a nationwide-nested population, such as in the Danish National Patient Register (DNPR) (9), making the

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sample size both large and complete. However, the quality of routinely collected data for administrative purposes may be questionable for use in epidemiological research. Validation is, as such, a prerequisite for using administrative discharge register-based data for this purpose. Validation of data within the DNPR has been performed in other medical areas (10-17). However, evaluation of data within the DNPR regarding PJI has not been performed before. We are not aware of any other studies investigating the validity of PJI diagnosis codes in any international administrative discharge registers (latest Medline search August 12, 2014).

The aim of this study was to evaluate the positive predictive value of the World Health Organization's International Classification of Disease 10th revision (ICD-10) diagnosis code of prosthesis-related infection in an administrative discharge registers, the DNPR, concerning hip PJI.

Methods

The study was performed as a cross-sectional study on data extracted from the DNPR on patients with a registration of performed surgical treatment for hip PJI. The purpose of the extraction was to 1) evaluate the T84.5 code and 2) to identify a cohort of patients treated for a chronic hip PJI (not pertaining to this study). The current study population included all patients registered in the DNRP with an ICD-10 discharge diagnosis code of T84.5 ("Infection and inflammatory reaction due to internal joint prosthesis") during the period between January 1, 2003 and December 31, 2008 (see Figure 1). Since T84.5 is not joint specific (18), we combined this diagnosis code with hip-joint specific surgical procedure codes, using the Nordic Medico-Statistical Committee (19) classification of surgical procedures (NCSP) code also registered in the DNPR (20). For description of applied NCSP codes see Figure 2. The first patient registration based on date of hospitalisation in the specified time frame was evaluated in this cross-sectional study. The DNPR (20) collects nationwide data on a day-to-day basis for all patients treated in non-psychiatric hospitals and all outpatient and emergency room departments at both public and private hospitals in Denmark. Registration of individual patients in the DNPR is based on a nationally adapted, unique, lifelong civil personal registration (CPR) number. The CPR number is assigned to all registered Danish citizens at birth or when granted citizenship (21). Since the beginning in 1977, registration in the DNPR has been performed electronically, and has previously been confirmed with a high completeness (20, 22). As of 1994, ICD-10 coding was applied when reporting discharge diagnosis codes to the register. The NCSP was introduced into the DNPR in 1996 (20). The DNPR contains information on date of admission and discharge, ICD-10 diagnosis and NCSP procedures performed for every single hospital contact a Danish citizen has for life. Reporting to the DNPR is mandatory by law.

We only included patients operated at selected departments of orthopaedic surgery associated with an existing research collaborative (23). These departments (n = 11) performed approximately 33% of all primary total HJR and 37% of all revision total HJR surgery in Denmark in 2008 (24).

Individual medical records of the identified patients were retrieved and were manually reviewed by 1 of the authors (JL). These medical records consisted of both paper records and electronic medical database systems pertaining to that individual hospital, as no standardised national archive system is employed to date. All data registered were sought in the original format if possible.

A diagnosis of PJI used in this study was adapted to Danish conditions by the authors based on the definition of PJI published by the workgroup of the American Musculoskeletal Infection Society (see Fig. 3) (25). In particular, the utilisation of the principle described by Kamme and Lindberg (26) in securing relevant tissue biopsies has been applied in all the centres in this study in the defined time frame and thus this principle was applied in the definition of PJI. Also, peroperative histopathology and synovial fluid analysis was not routinely performed in Denmark in the diagnostic set-up of PJI in the defined time frame and so not incorporated in the definition of PJI.

Medical record data were registered in Epidata 3.1 (EpiData Assoc., Odense, DK), a free software, which allows controlled data entry and data documentation. From the DNPR, information on ICD-10 and NCSP codes were merged with the medical record data by CPR number. Study approval was obtained from The Danish Health and Medicines Authority (3-3013-129/1/KAHO) and the Danish Data Protection Agency (2010-41-4294).

Statistics

Positive predictive values (PPV), with 95% confidence intervals (95% CI), was calculated as simple proportions: the absolute number of patients with verified PJI for the specific coding combination divided by the absolute number of patients found in DNPR with the same coding combination. Stratification was made in relation to duration of symptoms, type of infection, hospital site and implant. STATA 11.2 (STATA corp. College Station, TX) was used for all data analysis.

Results

In all, 283 patients had an ICD-10 discharge diagnosis of T84.5 (see flow chart). There were 197 (70%) total hip replacements, of which 109 (55%) were primary prosthesis; 59 (21%) were hip hemiarthroplasties; 3 (1%) were resurfacing arthroplasties; 6 (2%) were osteosynthesis implants; 18 (7%) did not have a hip associated implant (e.g. resection arthroplasty). In 6 (2%) patients information was not available in the medical records to clarify the PJI diagnosis sufficiently (e.g. due to water damage of the paper records). We chose to include these patients as non-PJI to ensure detection of all potential false-positive diagnosis, as sensitivity analysis did not indicate a statistical impact on the PPV (data not presented). Of the 283 patients with a T84.5 diagnosis code, 240 were classified as true PJI after medical record review, corresponding to an overall PPV of 85% (95% CI 80-89). 194 patients had a T84.5 diagnosis code in combination with an infection-specific procedure code (see Figure 2 for definition), of which 167 were classified as true PJI corresponding to a PPV of 86% (95% CI 80-91). 89 had a T84.5 diagnosis code in combination with a noninfection-specific procedure code (see Fig. 2 for definition), of which 73 were classified as true PJI corresponding to PPV of 82% (95% CI: 72-89).

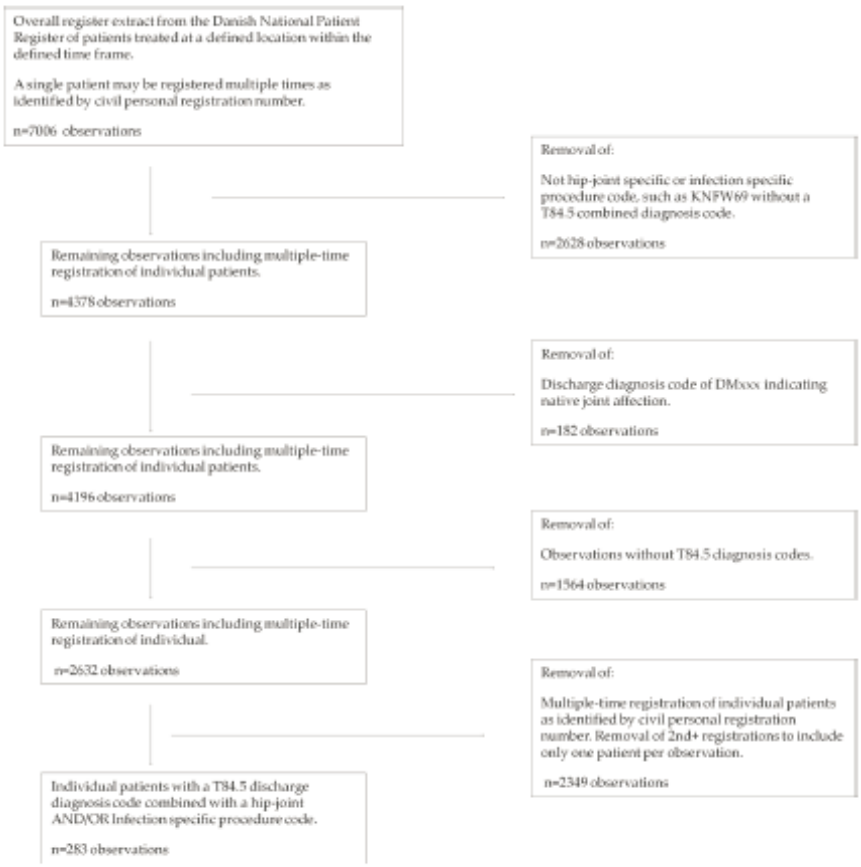

Fig. 1 - Flowchart. Inclusion of patient with a T84.5 discharge diagnosis code registered in the Danish National Patient Register between 2003-2008.

Results from the stratified analysis did not indicate that individual hospital, implant affected, duration of symptoms or type of infection influenced the PPV. The presence of a fistula or positive peroperative tissue biopsies increased the PPV to 92% (CI 95%: 86-96) and 94% (CI 95%: 90-97) respectively (Tab. I and Fig. 3).

Discussion

This study is the first to evaluate the positive predictive value of the only and commonly used discharge diagnosis code of prosthesis-related infection in administrative discharge registers. We found the PPV of the T84.5 ICD-10 code for hip PJI to be 85%. Infection-specific procedure codes (see Figure 2 for definition) did not enhance the PPV, and future studies may use the algorithm proposed in this study. Several studies have investigated the validity of ICD-10 codes discharge diagnose codes in the DNPR. Our results are in accordance to those previously found in other medical areas. Two studies on diseases diagnosed by simple, well-established laboratory measurements (anaemia by haemoglobin level and hyponatraemia by serum sodium value) showed excellent PPV, ranging from 92.5% to 95.4% (13, 17). Studies on more complicated disease processes with complex diagnostic criteria (acute stroke, acute coronary syndrome, atrial fibrillation and flutter, infection among cancer patient, infant respiratory distress syndrome and venous thromboembolism) have shown lower PPV in the range of 65.5%-92.6% (10-12, 14-16). It appears that more complex diagnoses, demanding elaborate diagnostic set-up, decreases the PPV of the discharge diagnosis code. PJI is an example of such a complicated disease with a potential elaborate diagnostic set-up. However, even a simple diagnosis based on a simple laboratory measurement test did not give a positive predictive value of 100%. Based on these studies it is clear that codes in administrative discharge registers are prone to misclassification on an administrative level either by the physician or administrative personnel in the registration process. This is also indicated in the present study where 6 patients with osteosynthesis related implants were incorrectly coded with the ICD-10 code T84.5 instead of T84.6 ("Infection and inflammatory reaction due to internal fixation device [any site]"). At what level this misclassification occurred in the current study is not available, but the case is illustrative. The magnitude and direction of bias due to misclassification must be evaluated on a study-to-study basis. Examples of the impact of misclassification can be evaluated in light of previous studies on PJI, based on single-source register data. Based on

KNF Cxx: Secondary prosthetic replacement of hip joint

KNF G09: Excision arthroplasty of hip joint

KNF G19: Interposition arthroplasty of hip joint

KNF G29: Other arthroplasty of hip joint without prosthetic replacement

KNF S19: Incision and debridement of infection of hip joint

KNF S49: Incision and debridement of infection of hip joint with introduction of therapeutic agent

KNF U0x: Removal of a partial prosthesis from hip joint

KNF U1x: Removal of a total prosthesis from hip joint

KNF U89: Removal of therapeutic implant in treatment of infection of hip or femur

KNF W69: Reoperation for deep infection in surgery of hip of thigh

Description:

The first three letters describe placement in the procedural hierarchy in descending order. K denotes *classification of surgery*; N denotes *musculoskeletal procedures*; F denotes *procedures on hip and femur*; x in the number denotes that more numbers may be applied to that position, e.g. KNFC20 is a cementless total hip arthroplasty and KNFC40 is a cemented total hip arthroplasty. In this case, all available combination has been applied in the search.

KNFS 19, KNFS49, KNFU89 and KNFW69 are infection-specific codes. The remaining codes are noninfection-specific. Infection-specific do not pertain exclusively to prosthesis infections, but can also be used for instance in native joint infection.

Fig. 2 - Textbox 1. Definition of The Nordic Medico-Statistical Committee classification of surgical procedures version 1.15 applied in the Danish National Patient Register search.

The US. Medicare 5% sample claim database, 1 study aimed at identifying co-morbid conditions, that could affected the risk of PJI (5). An example from this study of the effect misclassification of co-morbidities is alcohol abuse, which was found not to be statistically associated to PJI (crude relative risk 2.09, p-value 0.0566). Assuming patients, who abused alcohol, did not report this in a sufficient manner or were simply not registered appropriately by the medical personal, this would result in a nondifferential misclassification, which would bias the association toward null (27). In this particular study, alcohol abuse was not identified as a risk factor for developing PJI, when in fact it may present a direct or surrogate risk factor for developing PJI. A limitation, duly noted by the authors, was the possible lack of precise correlation between clinical records and the register data. The degree of misclassification must be taken into account when clinical advisory infer on data accumulated in administrative discharge registers.

Another study, based on data from the US. National Hospital Discharge Survey, concluded that PJI hospitalisations in the United States of America increased dramatically towards 2004 (6). The potential reasons noted by the authors were an increase in absolute number of prosthetic joints, a genuine increase in infection rate or both. No comments were made on the quality of the native data, and the potential misclassification would have on the result.

TABLE I - Stratified analysis of patients identified with the ICD-10 discharge diagnosis code T84.5 in the Danish National Patient Registry from 2003-2008

Variables (n = number)*	PPV %	95% CI	Number with confirmed PJI
Implant affected			
THA (n = 197)	94	90-97	185
HHA (n = 59)	88	77-95	52
Type of infection**			
Acute (n = 123)	96	91-99	118
Acute haematogenous (n = 26)	92	75-99	24
Chronic (n = 102)	91	84-96	93
Aseptic revision (n = 5)	100	48-100	5
Duration of symptoms			
<4 weeks (n = 158)	91	86-95	144
>4 weeks (n = 114)	83	75-90	95
Definition of infection†			
Category A (n = 139)	92	86-96	128
Category B (n = 176)	94	90-97	166
Not Category A & B (n = 66)	59	46-71	39
Hospital			
1 (n = 84)	81	71-89	68
2 (n = 54)	89	77-96	48
3 (n = 51)	82	69-92	42
4 (n = 29)	76	56-90	22
5 (n = 19)	89	69-99	17
6 (n = 18)	100	81-100	18
7 (n = 17)	88	64-99	15
8 (n = 11)	91	59-99	10

*The sum of the number identified may not add up to the total 283 identified patients due to missing/non-selected information.
**Acute = postoperative infection within 6 weeks of latest surgery; Acute haematogenous infection = symptom duration less than 4 weeks and later than 6 weeks of latest surgery with relevant extra-articular focus; Chronic infection = later than 6 weeks of latest surgery and not acute haematogenous infection; Aseptic revision = planned aseptic revision with positive growth of tissue biopsies.
†See Figure 2 for definition.
Abbreviations: THA = total hip arthroplasty; HHA = hemi-hip arthroplasty; PPV = positive predictive value; CI = confidence interval; PJI = periprosthetic joint infection.

Assuming hip surgeons awareness of coding PJI correctly increases over time (this could be due to a variety of reasons, not further elaborated here), then the reported increase is not (only) an actual increase in PJI, but potentially also in the praxis of correctly coding PJI.

In the present study, the T84.5 code appears to capture a wide range of conditions, and this must be kept in

Periprosthetic Hip Joint Infection were defined as:

- Category A:
  - Fistula to the prosthesis
- Category B:
  - Growth of identical microorganism in 3-5 of 5 separately taken per-operative tissue bi
  - (the Kamme-Lindberg principle)
- Category C:
  - 3 or more of the following criteria:
  - Growth of microorganism in cultures from joint fluid aspiration
  - Growth of microorganism in per-operative tissue biopsies not defined as category B.
  - Visual pus or purulent fluid during exchange procedure (surgeon's description)
  - Radionuclide imaging procedure indicating infection
  - Elevated C-Reactive Protein AND/OR Erythrocyte Sedimentation Rate
  - Conventional X-ray of the hip indicating infection

Fig. 3 - Textbox 2. Definition of Periprosthetic Hip Joint Infection used in the investigation of the T84.5 discharge diagnosis code in the Danish National Patient Register.

mind, when applying this code to a study based on a single-source data register. For instance the cumulative mortality rate is likely to differ among subgroups captured by this code, such as a younger patient with an acute PJI following a primary total hip replacement compared to an elderly patient with a chronic PJI in a hemi-hip replacement following a fracture to the femoral neck. The T84.5 code does not differentiate between these differences in demographics.

This study has some weaknesses. The data were only collected by a single investigator. However software was used, which allowed controlled data entry and documentation minimising the risk of typing errors. The interpretation on whether the patients included in this study, indeed suffered a PJI, was also performed by a single investigator and done retrospectively. But *a* priori defined PJI criteria were applied to limit subjective evaluation. However, an important concern, also recently debated at the International consensus meeting on Periprosthetic joint infection in Philadelphia, USA (https://www.efort.org/wp-content/uploads/2013/10/Philadelphia_Consensus.pdf: accessed August 13, 2014) is the lack of a uniform PJI diagnosis. Presence of a fistula or positive cultures (with wide diversity in techniques applied (28)) is believed to be key aspects in diagnosing PJI, and the surgeon will be aware to code correctly in these circumstances. More difficult however, are the cases where the surgeon has to make a clinical decision on whether an infection is present in the absence of a fistula or positive cultures. This is illustrated in the stratified analysis, where a diagnosis by existence of a fistula or positive cultures yielded much higher PPV (Tab. I). As the medical records were retrospectively evaluated, important information pertaining to the PJI criteria may not have been registered by the surgeon at time of treatment. This information bias could skew the PPV found in the current study. Also, we chose to include spacer/Girdlestone situation as non-PJI. These were in the majority amongst cases of previous PJI revisions, but in the context of this cross-sectional study, not appropriately defined as PJI. The lack of correct coding on the first revision of these procedures is not within the limits of this study to investigate. This study can only conclude on the PPV for patients registered in the period 2003-2008 in the DNPR, as coding habits may differ outside this period and register. Also this study only evaluates patient with active surgical treatment performed as a NCSP code was necessary for entry in the study. Patients not surgically treated, e.g. kept on suppressive antibiotic treatment, are not included.

A strength of this study is that revision surgery following THA is not centralised in Denmark. Thus revision is performed both locally and at tertiary referral centres, and based on the stratified analysis the coding habits of the hip surgeons appear uniform per individual hospital. The geographical distribution of the involved centres is believed to ensure external, international validity and comparability. We believe the conclusions made in this study are applicable, also internationally to other administrative discharge registers, however, a validation of the individual registers is needed to be certain.

We conclude that data on hip PJI obtained from administrative registers are a potential valuable single-source of information, but the discharge diagnosis code should be used with caution in medical research due to inherent misclassification. We believe that the ICD-10 code T84.5 in combination with a NCSP procedure code can be of use in future single-source register based studies, but preferably should be used in combination with alternate data sources to ensure higher validity.

Disclosures

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Conflict of interest: None.

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Paper III

Estimating re-infection rates by competing risk analysis following treatment for chronic periprosthetic hip joint infection in a non-selected multi-centre population.

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Abstract
Limited information is available regarding the prognosis of patients treated for chronic periprosthetic hip joint infection in a multi-centre setting. Furthermore, most available studies has not taken advantage of the available longitudinal data and time-to-event analysis when evaluating the prognosis. In addition competing risk analysis are rarely used. We therefore estimated the rate of re-infection of patients treated in a multi-centre setting for chronic periprosthetic hip joint infection in the presence of the competing events, death and open aseptic revision. We identified 130 patients treated for chronic periprosthetic hip joint infection across the participating centres. Follow-up was performed at minimum 5 years. The 5-year cumulative incidence rate of re-infection were found to be 14.7 % (95%CI 9.3-21.4). The 5-year survival rate was 68% (95%CI 59-75). We believe the presented way of analyzing data is recommendable in future studies on prognosis following treatment for chronic periprosthetic hip joint infection. We found a high mortality rate in our study population and we plan to conduct further mortality incidence analysis in near future.

Introduction

Periprosthetic hip joint infection (PJI) continues to be a feared complication more than 5 decades after the introduction of modern era hip joint replacements (HJR) with a 5-year incidence rate exceeding 1%[1].

Most studies on the prognosis following treatment for chronic PJI reports on selected patients following non-controlled treatment procedures[2], and only limited information is available on the outcome of a non-selected sample of patients with hip PJI[3]. The availability of information on non-selected population samples is very important in comparison of results across treatment centres and strategies, to avoid selection bias[2].

Currently, *gold-standard* in treatment of chronic PJI remain a delayed reimplantation procedure, often referred to as a two-stage revision[4]. Previous studies on the prognosis following two-stage revision, reports risk estimates of re-infection near 10%[2]. Risk estimates represent a simple way of reporting data, however to optimize the use of all available patient data from longitudinal studies, time-to-event analysis can be performed. However, only a limited number of studies on the prognosis following treatment for chronic PJI use this concept[5-7].

Competing events, such as death, could however influence reported risk estimates as emphasized by Berend and colleagues[8], and also influence time-to-event analysis, inadvertently leading to biased estimates[9]. In order to avoid bias, cumulative incidence rates should be calculated, treating death and/or other relevant events as competing events[9].

To our knowledge, long-term follow-up has never before been reported by competing risk analysis in a non-selected, multi-centre, population following treatment of chronic PJI.

Our primary aim was to investigate the prognosis of chronic infections in HJR with focus on re-infection in the presence of competing events.

Patients and Methods

This study was performed as a multi-centre longitudinal prognosis study by establishment of a historical cohort of patients undergoing treatment for a chronic hip PJI.

Study approval was obtained from The Danish Health and Medicines Authority (3-3013-129/1/KAHO) and the Danish Data Protection agency (2010-41-4294).

Study Methods:

The study cohort was established by identifying patients registered in the Danish National Patient Registry (DNPR) with treatment performed for a chronic hip PJI at participating departments of orthopaedic surgery.

A diagnosis of chronic hip PJI was adapted by the authors from the definition published by the workgroup of the American Musculoskeletal Infection Society[10], and defined as chronic by symptom duration for more than 4 weeks[11].

The definition used in this study is shown in Figure 1. The inclusion period ran between January 1st. 2003 and December 31st. 2008.

The DNPR electronically collects nationwide data on a mandatory-by-law day-to-day basis for all patient treated at public and private hospitals in Denmark. Registration of

individual patients in the DNPR is based on a nationally adapted, unique, lifelong civil personal registration *(CPR)* number. The *CPR* number is assigned to all registered Danish citizens at birth or when granted citizenship[12,13].
The participating departments of orthopaedic surgery were chosen from an existing research collaboration[14]. These departments (Aalborg, Aarhus, Gentofte, Hvidovre, North-Zealand Hospitals, Silkeborg, Vejle, Viborg) performed approximately 33% of all primary HJR (7998 performed nationwide) and 37 % of all revision HJR (1304 performed nationwide) registered in the Danish Hip Register in 2008, and with a relevant case-mix distribution believed to ensure national and international comparability[15].
Case-mix distribution in the Danish Hip Register is based on gender, age, hip disease, Charnley category and co-morbidity.
We define both an *index prosthesis* and *index procedure* in this study. The *index prosthesis* is defined as the HJR first treated for a chronic infection during the inclusion period. Prior infections were not cause for exclusion. The *index procedure* was defined as the first treatment procedure performed on the index prosthesis during the inclusion period, e.g. the procedure in which the infected implant was removed in a two-stage revision.
We excluded HJR with ongoing treatment for a chronic infection initiated prior to the inclusion period and not concluded at the initiation of the inclusion period.
The medical records were manually reviewed at the individual hospital by one of the authors (JL). All medical records were available. Medical record review was performed, at a minimum of 5 years after the index procedure.
Data extracted from the medical records included patient demographics and peri-operative aspects (see appendix). For each patient, data on comorbidity registered in a 5-year period prior to inclusion in the study was obtained from the DNPR[17] for the estimation of The Charlson Comorbidity severity *(CCS)* score[16].
Follow-up was done, via the CPR number, through the individual hospital patient-administrative-system and the nationwide electronic patient records "*e-journal*" (*http://www.regioner.dk/sundhed/sundheds-it/e-journal; accessed August 2014).* The nationwide electronic patient record was implemented nationally in 2009, and mandatorily registers all out-patient and hospital visits. Thus, we were able to investigate current vital status and further nationwide treatment in question for all included patients, with exact dates for these events.
The individual treatment strategy was performed at the discretion of the treating orthopaedic surgeon

Study population:
We identified a total of 461 patients with a World Health Organizations International Classification of Disease 10th revision (ICD-10) discharge diagnosis code T84.5 (*Infection and inflammatory reaction due to internal joint prosthesis*) in combination with a hip-joint specific Nordic Medico-Statistical Committee [14] classification of surgical procedures code or with a hip-joint infection-specific code independently of ICD-10 code (see appendix for description of codes).
Among the 461 identified patients, we verified 130 patients treated for a chronic hip PJI (see Fig. 1 for definition). The overall cohort of 130 patients were divided into two sub-

cohorts (see Fig. 2 for flow-chart). A *re-implanted cohort* (n=82) in which patients underwent re-implantation following a two-stage revision procedure. And a *Non re-implanted cohort* in which patients did not undergo a re-implantation following a two-stage revision procedure *(n=48).* The latter group consisted of patients with a permanent resection arthroplasty (n=35), patients kept on suppressive life-long antibiotics (n=1), patients with a direct exchange of implants (one-stage) (n=1) and patients with debridement performed (n=11).

Data analysis:
All cumulative incidence rates was estimated by competing risk analysis under the assumption of independent censoring[9]. Independent censoring means that a censored individual (e.g. due to death) should represent those still at risk without a systematic high or low risk of the main outcome occurring. The main outcome was re-infection with competing events, death and open aseptic revision. Competing-risk regression (Fine & Gray model) were fitted to examine predictor variables for the main outcome.
We used the Kaplan-Meier method to estimate cumulative all-cause mortality. A Cox regression model was fitted to examine predictor variables on mortality.
Due to the potential relevance of the predictor variables, we choose to collapse age into 5-year intervals, Body Mass Index (BMI, kg/m²) into groups of *underweight* (BMI <18.5), *normal weight* (BMI 18.5-25), *overweight* (BMI 25-30), *severe overweight* (BMI >30) and CCS score into groups of *0 co-morbidity*, *1 co-morbidity* (equally ranked), *2 co-morbidities* (equally ranked) or *3+ co-morbidities* (equally ranked).
In comparison between groups chi-squared test was used for dichotomized data, T-test for parametric continuous data and rank-sum test for categorical or non-parametric continuous data. QQ-plots were assessed for normality. Log-rank test was used to compare survival estimates. Proportional-Hazards assumption was assessed graphically. STATA 11.2 (STATA corp. College Station, TX) were used for all data analysis.

Results
Of the 130 patients verified with a chronic hip PJI, 48 could be classified as a category A PJI, 95 as a category B PJI (of which 37 were also category A) and 81 as a category C PJI (of which 57 were also category A and/or B). 10 patients could not be classified as Category A-C, but were nonetheless defined as chronic PJI based on their individual medical record review, (e.g. computer tomography showed an abscess in intimate relation to the hip joint and pre-operative hip aspiration grew *Staphylococcus aureus*).
The index prosthesis had been in situ for a minimum of 7 weeks for all 130 patients.
Baseline demographic data of the 130 patients are reported in table 1.
Following the index procedure, 53 patients (41%) had a spacer in situ, 64 patients (50%) had a resection arthroplasty and 13 patients (9%) maintained a HJR.
Reimplantation of a revision HJR in the *Re-implanted Cohort* was performed after a median period of 14 weeks (iqr 10-18).
We found a significant baseline difference in age, CCS score, BMI, HgB and ASA score indicating that the *Non re-implanted Cohort* was older and had poorer general health than the *Re-implanted Cohort* (see table 1).

The sub-cohorts did not differ in relevant clinical aspects in regards to peri-operative parameters (see table 2).
It is noteworthy that the average blood loss was 1.7 liters (95% CI 1.5-1.9) and that over 90% of patients received blood transfusion post-operatively. Only 2 patients (2%) had post-operative ipsilateral nerve affection.
Thirty-two patients did not grow a microorganism, of these, 11 (32%) had a fistula(see table 3).
In total 26 (20%) of the 130 patients were registered as re-infected following treatment of the index prosthesis (definition in figure 1 was applied). Of the 26 re-infections 17 could be defined as category A PJI, 18 as category B PJI (6 not A) and 3 as category C PJI. There were no registered re-infections beyond 6 years of follow-up (see time-to-event analysis).

Time-to-event analysis
The overall 5-year cumulative incidence rate of re-infection was 14.7 % (95%CI 9.3-21.4). The 5-year cumulative incidence rate in the *re-implanted cohort* was 14.6 % (95%CI 8.0-23.1) and in the *non re-implanted cohort* 14.9 % (95%CI 6.5-26.4) (See figure 3A-c). This difference were non-significant (p-value 0.89).
None of the examined variables in the competing risk regression modeling were strongly identified as uni-variate predictors of re-infection (see table 4). After adjusting for age group, CCS, ASA, index HJR, and PJI category, female gender was associated to a higher cumulated incidence rate of re-infection (p-value 0.03).
Survival curves for all-cause mortality are shown in figure 4A+B. The overall 1-year survival rate was 92% (95%CI 86-96). The 1-year survival rate in the *non re-implanted cohort* was 83% (95%CI 69-91) and in the *re-implanted cohort* 98% (95%CI 91-99). The overall 5-year survival rate was 68% (95%CI 59-75). The 5-year survival rate in the *non re-implanted cohort* was 45% (95%CI 30-58) and in the *re-implanted cohort* 82% (95%CI 71-89). In the 8th follow-up year the survival rate drops below 50%. Beyond this time frame, less than 25% of the patient population was followed.
A higher ASA score, higher CCS score, higher age at time of index procedure and being underweight compared to normal weight were independent predictors of mortality during the follow-up period(see table 5). Overweight, pre-operative hemoglobin level and gender did not independently affect mortality rates.
There was a significant difference in survival between the two sub-cohorts (hazard ratio 0.32, 95% CI 0.10-0.53 p-value <0.00001). After adjusting for confounding variables (gender, age group, ASA, CCS, underweight and pre-operative hemoglobin level), patients in the *non re-implanted cohort* still had a 25% higher, although non-significant, risk of dying compared to patients in the *re-implanted cohort* (adjusted hazard ratio 0.75; 95%CI 0.30-1.87; p-value 0.54).

Discussion

Competing risk analysis of longitudinal data on a non-selected population after treatment for chronic PJI has not been reported and we present our multi-centre result on 130 patients.

Aspects on Re-infection

For patients in the established cohorts the rates of re-infection at 5-year follow-up were near 15%. These take death and aseptic revision into account as competing events, and is in our opinion a more accurate estimate than those previously reported[2], as discussed further below.

One of the values of time-to-event analysis on data from longitudinal studies, is the possibility of evaluation of information obtained in the entire follow-up period. By inspection of fig. 3 it is clear, that the majority of patients develop re-infection within the first two years post-operatively. This trend is also found by others[7]. This indicates that the often used "minimum" follow-up period of 2 years following treatment for chronic PJI is a relevant time frame[6,8].

We found female gender to be the only predictors of re-infection based on our established sample population. Other studies[6,17] have highlighted gender, presence of a fistula (category A PJI), inadequate antimicrobial treatment, and microorganism as potential predictors of re-infection, but these results could not be confirmed by our study. Most studies are restricted to predictors of PJI following primary procedures, and the investigation of the predictors for re-infection following treatment for chronic PJI is somewhat inhibited by the relatively few cases.

The presented re-infection rates are more directly comparable to re-infection rates from studies on other treatment strategies, such as one-stage revision[8], as death is taken into account, which previously have been an analytic obstacle when comparing predominantly used revision strategies following chronic PJI[2].

Aspects on Mortality

We found a high mortality among the 130 patient. After the 8th follow-up year more than half of the sample population were deceased. However, we cannot comment on the causality of PJI and mortality rate. We simply do not have the cause of death, nor have we compared to a matched background population. Recent reports have nonetheless highlighted the potential increase in risk of mortality that PJI imposes on the patients[8,18,19]. Mortality rates between 26-48% at 5-year follow-up have been reported, and been found significantly different in comparison to patients undergoing aseptic revision[19]. It is plausible that a chronic PJI population is at increased risk of dying.

We plan on conducting a register based evaluation of the potential relationship in near future.

We found higher ASA score, higher CCS score, higher age at time of index procedure and being underweight compared to normal weight independent predictors of mortality. Other studies have found divergent results. Choi et al[19] identified only CCS score as

predictor of mortality following chronic PJI whereas ASA score, age, gender were not predictive. Of these only CCS score was repeatedly identified by Zmistowski[18] as independent predictor of mortality following chronic PJI but they also identified age as a predictor. Further investigation into these predictors is warranted on larger populations.

Aspects on the sub-cohorts

We found a significant difference between our established sub-cohorts with patients re-implanted being younger, with lower CCS, higher BMI, higher pre-operative hemoglobin level and lower ASA score indicating that patients undergoing re-implantation are a selected group of patients.

By inspection of the survival curve in fig. 4 it is clear that the *non re-implanted cohort* experience a rapid decline in survival. Pre-reimplantation mortality may bias results between treatment strategies. Whether patients are selected for a treatment strategy due to co-morbidities or risk of dying at the time of decision, or that patients simply die before offered a chance for re-implantation is beyond the scope of this report. But we concur with the notion of Berend and colleagues[8], that control of infection is not achieved if a patient is not re-implanted due to all causes, and that future reports should include a "worst-case" scenario.

This also includes an elaborate description of the overall sample from which the study population was assembled, to enable a more precise comparison between results from different centres and/or treatment strategies.

In our study population only 63% of the identified patients were re-implanted in a two-stage revision procedure. This could be interpreted as the existence of selection bias in the comparisons made between two-stage revision and one-stage revision[2]. Re-implantation rates previously reported lie between 69-92%[8,19,20] or not stated at all[5,6], and none of these illustrated by a flow chart. The cause of this wide range of patients re-implanted may pertain to the fact that our patient population is a non-selected sample, whereas in other studies patient are referred to tertiary referral centres reporting their experiences[5,6,20].

Analytic considerations

Simple risk estimates represent an easily apprehensible way of reporting data from longitudinal studies, but relevant prognostic information is hidden in the course of progression towards the estimates, and in the case of a main outcome of re-infection, mortality also bias the risk.

A recent study on 125 patients[5] reported a 5-year risk of re-infection of 4% (5 patients re-infected), but some patients died, and where not taken into account in the analysis. Assume, by chance, that the patients not re-infected all died before the 5-year follow-up, and the analysis remained the same. This would still give a 5-year risk of 4%. You cannot "die" unless you experience a re-infection first.

In time-to-event analysis by the Kaplan-Meier method, which is used in studies on prognosis following two-stage revision[5,6], it is assumed that an individual being censored, is at the same risk of developing the main outcome after censoring, as those not yet censored. In the concrete example of the main outcome of re-infection, even after death has occurred, the patient presumably still has the same risk of developing re-infection, as

those alive in the study. This violates the principle of independent censoring. Deceased patients will have a systematically "lower" risk of developing re-infection. The biased estimate can be visualized by analyzing the data obtained in our study. Figure 5 shows the *1-kaplan Meier* estimate compared with the competing risk estimate on our dataset. The difference in this study is not large, the ratio 0.87 (analysis not presented), but it is erroneously estimate nonetheless.
Acknowledging the fact that competing events can bias incidence rates[7], and henceforth perform competing risk analysis will lead to an increased quality of between-study comparison of re-infection rates following re-implantation in different treatment strategies and between different centres[5,6,8,20].

Methodological considerations
This study has some limitations. This is not a truly nested cohort, and the inherent register risk of misclassification exist. Patients, not registered appropriately, may be systematically better or worse, e.g. those not selected for surgery are likely systematically worse. To what degree this bias skew results cannot be defined within this study and this has to our knowledge never been investigated.
The small sample size is a limitation and p-values should be interpreted with caution due to the risk of significant findings by random variation.
Due to the retrospective nature of the study, information bias pertaining to information obtained in the medical records review may exist. CCS score is also potentially underestimated in this group, but the positive predictive value of the CCS score in the DNPR has previously been shown to be high[21].
Due to *immortal person time* bias in the *re-implanted cohort*, we estimated time-at-risk from date of re-implantation. *Immortal person time* is the time from removal of index HJR to re-implantation. During this time period patients cannot die. This leaves a theoretical disadvantage concerning mortality incidence rates, as the *re-implanted cohort* would implicitly be older by the time frame of the interim period. We did perform sensitivity analysis (data not presented) with and without immortal person time and the estimated rate differences were interpreted to be of no impact to the study conclusions.
Strengths of this study include the full spectrum investigation on a native flow of patients. Many centres and surgeons have been involved in the treatment of the sample population and the volume per surgeon is much less than that of reports originating from large tertiary referral centres[5-7,20].

Conclusions:
We found a cumulative incidence of re-infection just below 15% in the follow-up period regardless of sub-cohort. This is comparable to international results. But do indicate the need for overall improvement in the treatment of chronic hip PJI in Denmark. We found a high mortality rate in our sample population, but the causality of death and chronic PJI cannot be established in this current study. We plan to conduct further mortality incidence analysis in near future.
We believe this study indicates that bias exist when choosing patients fit for re-implantation, and that this must be taken into consideration when comparing result on different revision strategies. We believe the presented way of analyzing data is recommendable in studies on prognosis following treatment for chronic periprosthetic hip joint infection in light of this.

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Table 1. Baseline demographics of 130 patients treated for chronic hip PJI between 2003-2008.

Variable	Overall Cohort	Re-implanted	Non-reimplanted	p-value
Age in years Mean (95%CI)	71 (69-73)	68 (66-71)	76 (72-80)	0.0006
Age at time of death in years Mean (95% CI)	80 (77-83)	77 (73-81)	82 (79-86)	0.05
Male gender % (95%CI)	51 (42-59)	57 (46-68)	40 (26-55)	0.07
Excessive Alcohol consumption* % (95%CI)	10 (4-15)	12 (6-22)	4 (1-15)	0.16
Smoker % (95%CI)	26 (19-34)	25 (15-35)	29 (15-42)	0.64
Antithrombotic treatment % (95%CI)	30 (22-39)	32 (21-42)	29 (16-42)	0.76
SIRS at time of procedure˜ % (95%CI)	3 (0-6)	1 (0-4)	6 (1-13)	0.11
Index HJR is a revision prosthesis % (95%CI)	25 (17-33)	25 (15-35)	24 (11-37)	0.86
Number of prior operations to index hip Median (IQR)	2 (1-3)	2 (1-3)	2 (1-4)	0.06
CCS Median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	0.005
In situ duration of index prosthesis in weeks Median (IQR)	89 (37-241)	88 (38-229)	91 (27-317)	0.73
BMI in kg/m² Mean (95% CI)	26.0 (25.0-27.0)	26.9 (25.7-28.0)	24.4 (22.8-25.9)	0.005
BMI groups % (95%CI)				
<18.5	4 (0-7)	4 (0-8)	5 (0-11)	0.001
18.5-25	46 (37-54)	33 (23-44)	68 (54-82)	
25-30	29 (21-38)	40 (29-50)	11 (2-21)	
>30	21 (14-28)	23 (14-33)	16 (5-27)	
Pre-operative hemoglobin in mmol/l Mean (95% CI)	7.3 (7.1-7.5)	7.6 (7.4-7.8)	6.8 (6.5-7.2)	0.0004
ASA score Median (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	0.0001

Follow-up in years Median (IQR)	8 (6-9)	7.9 (6.2-9.3)	8.7 (6.9-10.4)	0.03

SIRS: Systemic Inflammatory Response Syndrome; CI: confidence interval; IQR: Interquartile Range, Q1-Q3; ASA: American Society of Anesthesiologists score; BMI: Body Mass Index; CCS: Charlson Comorbidity severity score; HJR: Hip Joint Replacement;
* More than 21 units/week for men and 14 units/week for women.
˜ 2 or more of: temperature >38.0/<36.0, Heart rate >90/min, Respiratory Frequency >20/min, White blood cell count >$12.0x10^9$/<$4.0x10^9$

Table 2. Peri-operative variables of 130 patients treated for chronic hip PJI between 2003-2008.

Variable	Overall Cohort	Re-implanted	Non-reimplanted	p-value
Femoral osteotomi performed % (95%CI)	48 (39-56)	52 (41-63)	38 (24-52)	0.12
Stem loose % (95%CI)	22 (15-29)	28 (18-38)	11 (2-20)	0.02
Cup loose % (95%CI)	28 (19-36)	22(12-31)	40 (23-57)	0.05
Duration of surgery at initial procedure in minutes mean (95%CI)	148 (137-159)	156 (141-170)	133 (115-151)	0.05
Blood loss at initial procedure in liters mean (95%CI)	1.7 (1.5-1.9)	1.8 (1.6-2.1)	1.6 (1.3-2.0)	0.42
Anesthesia General Spinal Other % (95%CI)	 58 (49-66) 41 (33-50) 1 (0-2)	 57 (46-68) 42 (31-53) 1 (0-4)	 60 (45-74) 40 (26-55) No obs.	 0.72
Neurological deficits in the ipsilateral extremity following index treatment % (95%CI)	2 (0-4)	2 (0-6)	No obs.	0.30
Blood transfusion following index treatment % (95%CI)	92 (87-97)	91 (85-95)	94 (86-100)	0.63
Number of blood transfusions median (IQR)	4 (3-6)	4 (3-6)	4 (2-7)	0.75
Length of stay following index treatment in days median (IQR)	25 (18-41)	24 (18-39)	25 (19-46)	0.67

Abbreviation: CI: confidence interval; IQR: Interquartile Range, Q1-Q3.

Table 3. Microorganism cultured in 130 patients treated for chronic hip PJI between 2003-2008.

Microorganism cultured	Number (%)
Culture negative	32 (25)
Staphylococcus aureus	29 (22)
Coagulase-negative *Staphylococcus species*	26 (20)
Streptococcus species	12 (9)
Enterococcus faecalis	8 (6)
Miscellaneous species	8 (6)
Proteus species	5 (4)
Polymicrobial	5 (4)
Pseudomonas aeruginosa	2 (2)
No information available	3 (2)

Table 4. Competing risk regression (Fine & Gray model) fitted on selected variables for assessment of influence on the cumulative incidence of re-infection after treatment for chronic hip PJI in 130 patients.

Variable			Sub-Hazard Ratio	95% Confidence Interval	p-value
Gender	Overall	Crude	2.17	0.87-5.41	0.10
Female		Adjusted	2.90	1.14-7.36	0.03
vs.	Re-implanted	Crude	1.12	0.38-3.31	0.83
Male		Adjusted	1.28	0.45-3.68	0.64
	Non re-implanted	Crude	∞	-	<0.0001
		Adjusted	∞	-	<0.0001
Age *	Overall	Crude	0.92	0.76-1.13	0.43
		Adjusted	0.84	0.69-1.02	0.07
	Re-implanted	Crude	0.79	0.59-1.06	0.12
		Adjusted	0.79	0.58-1.07	0.13
	Non re-implanted	Crude	1.06	0.82-1.36	0.67
		Adjusted	0.72	0.39-1.31	0.28
CCS*	Overall	Crude	1.17	0.78-1.77	0.45
		Adjusted	1.43	0.89-2.31	0.14
	Re-implanted	Crude	1.63	0.90-2.96	0.11
		Adjusted	2.01	0.87-4.64	0.10
	Non re-implanted	Crude	0.80	0.45-1.42	0.45
		Adjusted	0.89	0.45-1.75	0.73
ASA	Overall	Crude	0.59	0.33-1.05	0.07
		Adjusted	0.53	0.27-1.07	0.08
	Re-implanted	Crude	0.83	0.34-2.00	0.67
		Adjusted	0.47	0.13-1.78	0.27
	Non re-implanted	Crude	0.31	0.11-0.81	0.02
		Adjusted	0.49	0.16-1.54	0.23
BMI*					
Normal	Overall	Crude	4.30	0.94-19.64	0.06
vs.		Adjusted	1.24	0.16-9.87	0.84
Underweight	Re-implanted	Crude	4.99	0.52-47.64	0.16
		Adjusted	1.33	0.08-22.00	0.84
	Non re-implanted	Crude	4.54	0.59-34.73	0.15
		Adjusted	14.26	0.07-2756.57	0.32
Normal	Overall	Crude	1.46	0.87-2.46	0.15
vs.		Adjusted	1.33	0.73-2,39	0.35

Overweight	Re-implanted	Crude	1.68	0.84-3.36	0.14
		Adjusted	1,28	0.58-2.84	0.54
	Non re-implanted	Crude	1.26	0.58-2.74	0.55
		Adjusted	0.90	0.38-2.12	0.81
Index HJR	Overall	Crude	0.35	0.08-1.56	0.17
Revision		Adjusted	0.36	0.07-1.79	0.21
vs.	Re-implanted	Crude	0.60	0.13-2.83	0.52
Primary		Adjusted	0.78	0.13-4.78	0.79
	Non re-implanted	Crude	≈	-	<0.0001
		adjusted	≈	-	<0.0001
PJIcatA	Overall	Crude	0.81	0.33-1.99	0.64
Yes		Adjusted	0.90	0.34-2.36	0.83
vs.	Re-implanted	Crude	0.42	0.10-1.79	0.24
No		Adjusted	0.45	0.08-2.47	0.36
	Non re-implanted	Crude	1.58	0.39-6.41	0.53
		adjusted	1.37	0.24-7.94	0.72
PJIcatB	Overall	Crude	0.70	0.28-1.72	0.44
Yes		Adjusted	0.66	0.27-1.59	0.35
vs.	Re-implanted	Crude	0.87	0.27-2.79	0.81
No		Adjusted	0.79	0.23-2.66	0.70
	Non re-implanted	Crude	0.49	0.12-1.97	0.31
		adjusted	0.90	0.14-5.99	0.91

BMI: Body Mass Index; ASA: American Society of Anesthesiologists score; PJIcatA/B: Definition of Periprosthetic Joint Infection; HJR: Hip joint replacements.
All variables are adjusted for gender, age, CCS, ASA, index HJR, PJI category. Statistical significant p-values are depicted in bold.
*Collapsed variable: age in 5-year intervals; BMI *underweight* (<18.5), *normal weight* (18.5-25), *overweight (* >25); CCS *0 co-morbidity*, *1 co-morbidity* (equally ranked), *2 co-morbidities* (equally ranked) ,*3+ co-morbidities* (equally ranked).
∞ No males in the *non re-implanted cohort* (n=19) were re-infected. The SHR is thus infinite high, indicating that female gender is severely predictably for re-infection in the non re-implanted cohort. However, this cannot be quantified further.
≈ No patients with a revision index prosthesis in the *non re-implanted cohort* (n=10) were re-infected. The SHR is thus infinite low, indicating that a primary HJR is severely predictably for re-infection in the non re-implanted cohort. However, this cannot be quantified further.

Table 5. Cox regression model fitted on selected predictive variables for assessment of influence on survival regardless of treatment received in 130 patients treated for chronic hip PJI between 2003-2008.

Variable		Hazard Ratio	95% Confidence Interval	P-value
CCS*	Crude	1.83	1.46-2.29	<0.0001
	Adjusted	1.68	1.31-2.17	<0.0001
Gender	Crude	1.27	0.76-2.13	0.37
Female	Adjusted	0.97	0.53-1.77	0.93
vs.				
Male				
Age*	Crude	1.33	1.17-1.52	<0.0001
	Adjusted	1.29	1.11-1.50	0.001

BMI*				
Normal	Crude	2.30	0.81-6.55	0.12
vs.	Adjusted	13.97	3.44-56.71	0.002
Underweight				
Normal				
vs.	Crude			
Overweight	Adjusted	0.68	0.48-0.97	0.03
		0.70	0.46-1.06	0.09
HgB	Crude	0.63	0.48-0.84	0.002
	Adjusted	0.94	0.70-1.32	0.72
ASA	Crude	3.63	2.26-5.84	<0.0001
	Adjusted	2.69	1.50-4.82	0.001

HgB: pre-operative hemoglobin level; ASA: American Society of Anesthesiologists score; BMI: Body Mass Index CCS: Charlson Comorbidity severity score

*Collapsed variable: age in 5-year intervals; BMI *underweight* (<18.5), *normal weight* (18.5-25), *overweight (* >25); CCS *0 co-morbidity*, *1 co-morbidity* (equally ranked), *2 co-morbidities* (equally ranked) ,*3+ co-morbidities* (equally ranked).

All variables are adjusted for Gender, Age, ASA, CCS, HgB.

Figure 1. Definition of Periprosthetic Hip Joint Infection used in the investigation of chronic hip PJI between 2003-2008.

- Category A:

  Fistula to the prosthesis

- Category B:

  Growth of identical microorganism in 3-5 of 5 separately taken per-operative tissue biopsies

  (the Kamme-Lindberg principle)

- Category C:

  or more of the following criteria:

  - Growth of microorganism in cultures from joint fluid aspiration
  - Growth of microorganism in per-operative tissue biopsies not defined as category B.
  - Visual pus or purulent fluid during exchange procedure (surgeon's description)
  - Radionuclide imaging procedure indicating infection

Figure 2. Flowchart

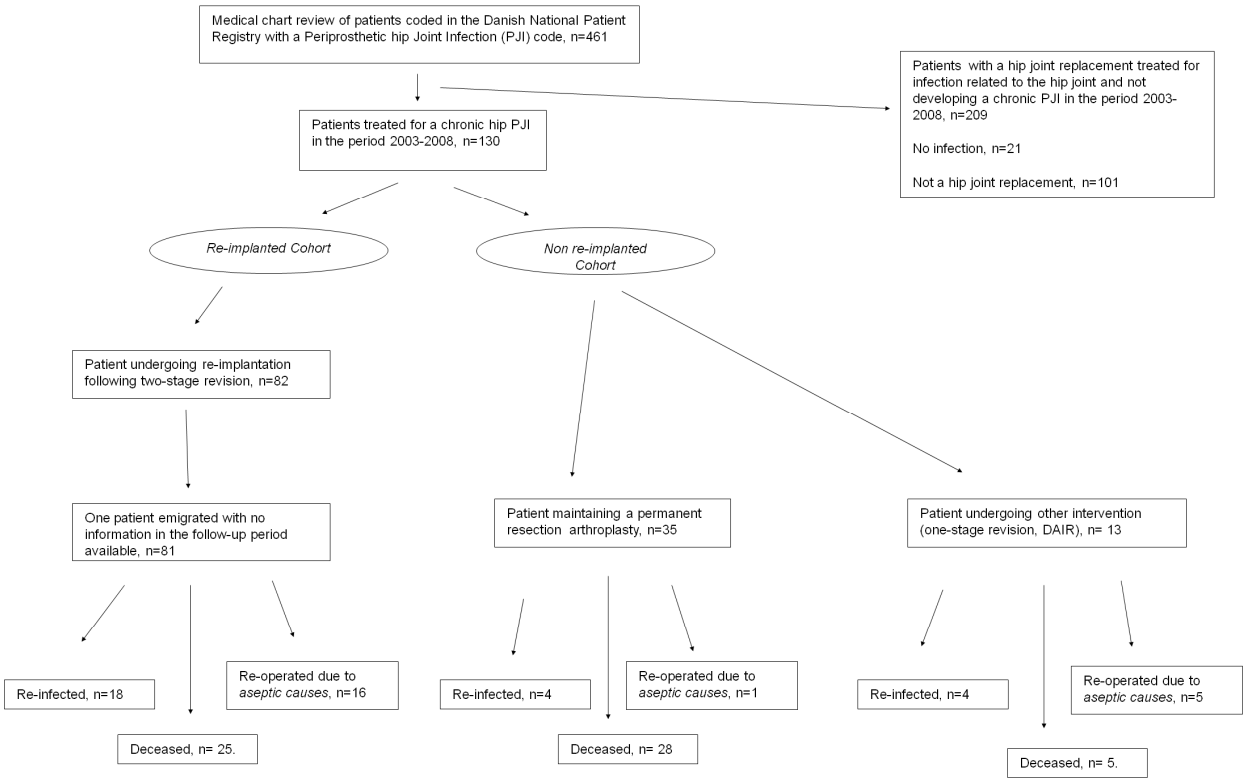


Fig 3A: Cumulative incidence curve on re-infection after treatment for chronic periprosthetic hip joint infection in 130 patients in the presence of competing events, death and open aseptic revision.

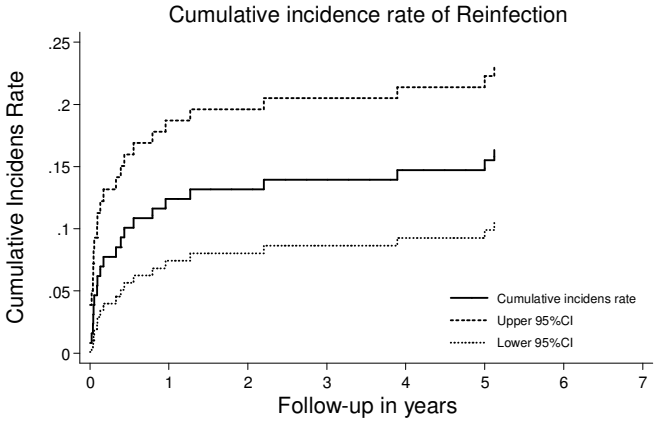


Fig 3B: Cumulative incidence curve on re-infection after treatment for chronic periprosthetic hip joint infection in 48 patients not undergoing re-implantation following a two-stage revision strategy in the presence of competing events, death and open aseptic revision.

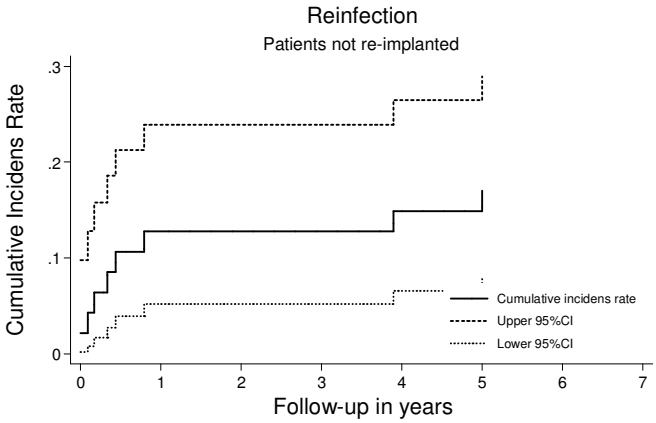


Fig 3C: Cumulative incidence curve on re-infection after treatment for chronic periprosthetic hip joint infection in 81 patients undergoing re-implantation following a two-stage revision strategy in the presence of competing events, death and open aseptic revision.

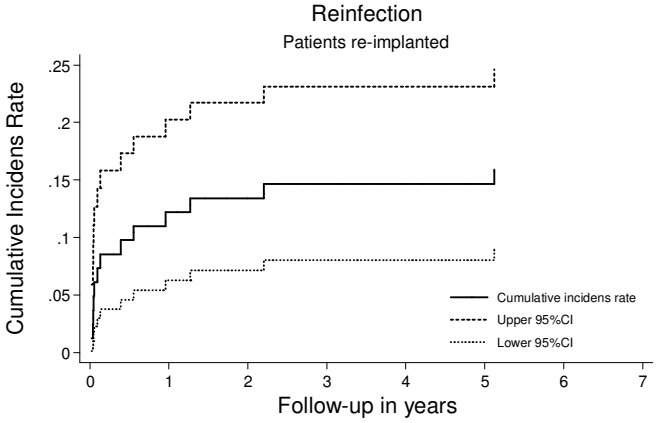


Fig 4A: Survival curve after treatment for chronic periprosthetic hip joint infection in 130 patients.

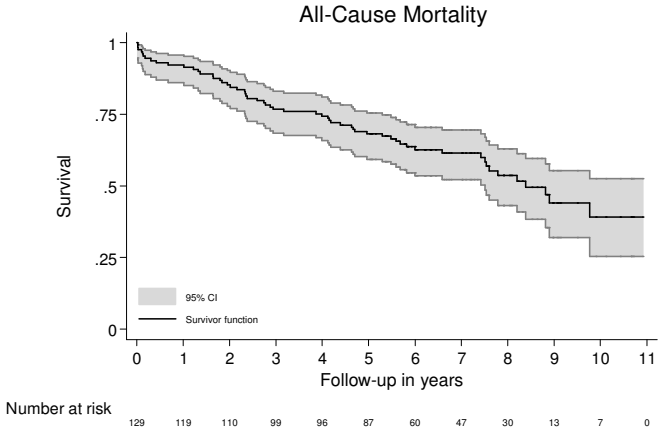


Fig 4B: Survival curves after treatment for chronic periprosthetic hip joint infection in 81 patients undergoing re-implantation following a two-stage revision strategy and 48 patients not undergoing re-implantation following a two-stage revision strategy.

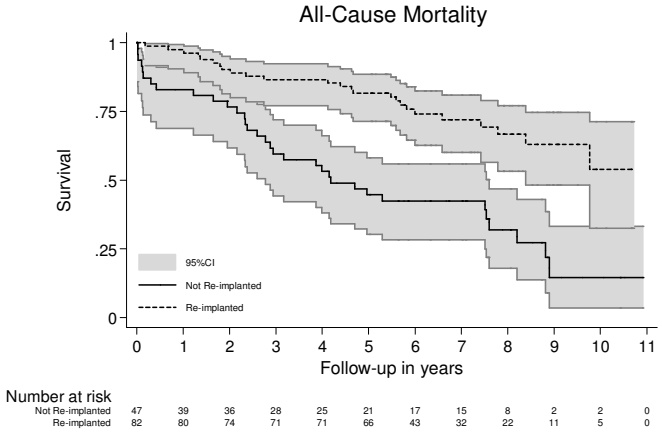
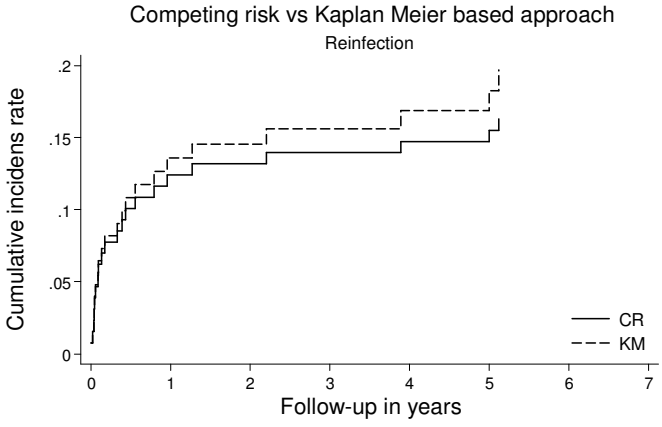


Fig 5: Competing risk analysis vs. 1-Kaplan-Meier estimate on re-infection after treatment for chronic periprosthetic hip joint infection in 130 patients.



Appendix:

KNF Cxx:	Secondary prosthetic replacement of hip joint
KNF G09:	Excision arthroplasty of hip joint
KNF G19:	Interposition arthroplasty of hip joint
KNF G29:	Other arthroplasty of hip joint without prosthetic replacement
KNF S19:	Incision and debridement of infection of hip joint
KNF S49:	Incision and debridement of infection of hip joint with introduction of therapeutic agent
KNF U0x:	Removal of a partial prosthesis from hip joint
KNF U1x:	Removal of a total prosthesis from hip joint
KNF U89:	Removal of therapeutic implant in treatment of infection of hip or femur
KNF W69:	Reoperation for deep infection in surgery of hip of thigh

Description:
The first three letters describe placement in the procedural hierarchy in descending order. K denotes *classification of surgery*; N denotes *musculoskeletal procedures;* F denotes *procedures on hip and femur;* x in the number denotes that more numbers may be applied to that position, e.g. KNFC20 is a cementless total hip arthroplasty and KNFC40 is a cemented total hip arthroplasty. In this case, all available combination has been applied in the search.
KNFS 19 and KNFS49 are considered hip-joint infection-specific codes.

Data extracted from the individual medical records of 130 patients with a chronic Periprosthetic Hip Joint Infection.

Patient demographics:
Gender, Age, Side of affected hip, Presence of other Internal artificial implants, Consumption of alcohol, tobacco use, Medical treatment with anticoagulant drugs, weight, height, septic at time of index treatment, Antibiotic treatment prior to index treatment
PJI diagnosis:
Serology (SR, CRP, WBC), Nuclear or conventional imaging performed, pre-operative joint aspiration, history of fistula, per-operative biopsies
Demograhics of index HA:
Cause of insertion, date of insertion, revisions performed prior to index treatment, time from insertion to infection symptom debut, duration of symptoms, number of surgeries in the past to the affected hip
Index treatment:
date, surgeons description of sign of infection per-operative, is the stem or cup loose, is femoral osteotomi performed, surgical acess, total closure of skin incision performed, bleeding in ml during surgery, duration of operation, hip status after index treatment, in case of spacer insertion nature and cement used, placement of local antibiotics, Engh classification of the acetabulum if noted, Paprosky classification of femur if noted, type of anaestisia, per-operative complikations, ASA score, hgb pre-operatively, post-operative complications, per-operative cultures, blood transfusions performed, wound complications, newly arisen post-operative neural affections to the affected limp, duration of hospitalization.
Interim period (if applicable):
Complications to the spacer, other complications
Revision treatment (if applicable):
date of insertion of revision HA, type of HA inserted, per-operative bleeding, duration of surgery, allograft used, cerclage used, other internal osteosyntesis used, drainage used, painkathether used, flowroom used, Engh classification of the acetabulum if noted, Paprosky classification of femur if noted, type of anaestisia, per-operative complikations, per-operative cultures, blood transfusions performed, wound complications, newly arisen post-operative neural affections to the affected limp, duration of hospitalization, other complications.
Registration of re-infection (if applicable):
Date, Serology (SR, CRP, WBC), Nuclear or conventional imaging performed, pre-operative joint aspiration, present fistula, per-operative biopsies
Registration of aseptic revision (if applicable):
Date, cause
Registration of vital status:
Date, status.