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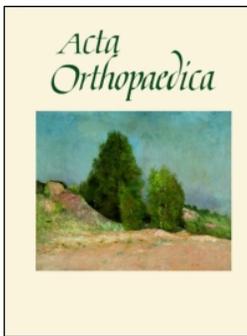
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Revision of infected knee arthroplasties in Denmark

Outcome of 105 partial revisions (open debridement and exchange of tibial insert) and 215 two-stage revisions

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Background and purpose — The surgical treatment of periprosthetic knee infection is generally either a partial revision procedure (open debridement and exchange of the tibial insert) or a 2-stage exchange arthroplasty procedure. We describe the failure rates of these procedures on a nationwide basis.

Patients and methods — 105 partial revisions (100 patients) and 215 potential 2-stage revision procedures (205 patients) performed due to infection from July 1, 2011 to June 30, 2013 were identified from the Danish Knee Arthroplasty Register (DKR). Failure was defined as surgically related death \leq 90 days postoperatively, re-revision due to infection, or not reaching the second stage for a planned 2-stage procedure within a median follow-up period of 3.2 (2.2–4.2) years.

Results — The failure rate of the partial revisions was 43%. 71 of the partial revisions (67%) were revisions of a primary prosthesis with a re-revision rate due to infection of 34%, as compared to 55% in revisions of a revision prosthesis ($p = 0.05$). The failure rate of the 2-stage revisions was 30%. Median time interval between stages was 84 (9–597) days. 117 (54%) of the 2-stage revisions were revisions of a primary prosthesis with a re-revision rate due to infection of 21%, as compared to 29% in revisions of a previously revised prosthesis ($p = 0.1$). Overall postoperative mortality was 0.6% in high-volume centers (> 30 procedures within 2 years) as opposed to 7% in the remaining centers ($p = 0.003$).

Interpretation — The failure rates of 43% after the partial revision procedures and 30% after the 2-stage revisions in combination with the higher mortality outside high-volume centers call for centralization and reconsideration of surgical strategies.

■

Aseptic revision knee arthroplasty is associated with low mortality and low postoperative morbidity (Lindberg-Larsen et al. 2014), but infected revision knee arthroplasty surgery is

associated with increased mortality, longer hospital stay, and higher re-admission rates (Choi and Bedair 2014, Kapadia et al. 2014). Furthermore, a recent systematic review (Masters et al. 2013) has found failure rates of infection eradication ranging from 0% to 41%. A 2-stage approach is the gold standard in surgical treatment of the chronic infected knee arthroplasty. This includes at least 2 hospitalizations and an interim period between surgeries with a potentially increased risk of associated diseases and reduced quality of life. According to the algorithms provided by European experts, the recommended interval between the first and second stage of a 2-stage revision arthroplasty due to infection is 2–6 weeks (Zimmerli and Ochsner 2003), whereas in the USA the interval often appears to be longer, e.g. 4–6 weeks of antibiotics with subsequent cessation of antibiotics for 2–8 weeks prior to reimplantation (Osmon et al. 2013, Parvizi et al. 2013). It is unknown which interval strategy is adhered to in Denmark. In other cases with early postoperative infections (< 4 weeks after implantation) or acute hematogenous infections with a less than 3-week duration of symptoms, implant salvage may be attempted using a less comprehensive surgical procedure with open debridement and polyethylene liner exchange (Osmon et al. 2013). However, this salvage procedure may be associated with even higher failure rates (Azzam et al. 2010, Gardner et al. 2011, Odum et al. 2011, Fehring et al. 2013).

There are limited nationwide data on the partial revision and 2-stage revision procedures performed for prosthetic knee infection and on outcomes related to them (Bengtson and Knutson 1991, Holmberg et al. 2015).

In this nationwide study, we determined failure rates for partial revision procedures (open debridement and exchange of tibial insert) and for 2-stage exchange arthroplasty procedures that were all performed due to infection.

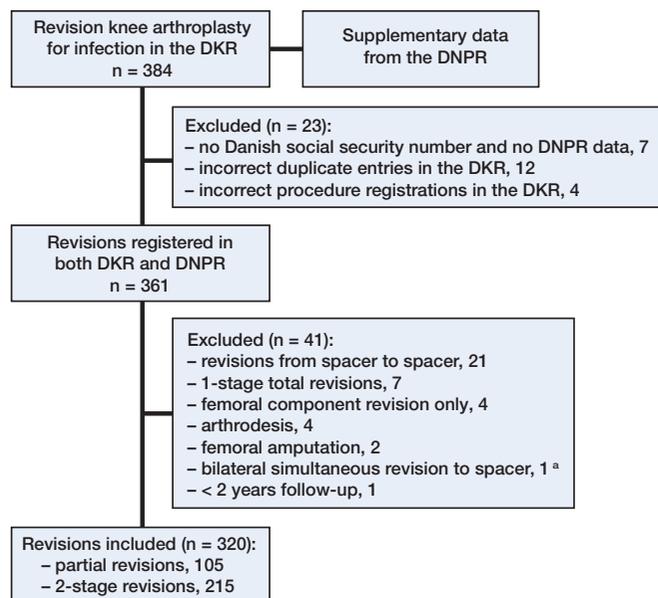


Figure 1. Selection of the study population. DNPR: the Danish National Patient Registry; DKR: the Danish Knee Arthroplasty Registry. ^a Registered as 2 procedures in the DKR and both were excluded.

Patients and methods

This study was based on prospectively collected data from the Danish Knee Arthroplasty Register (DKR 2012, DKR 2013). All revision knee arthroplasty procedures performed due to infection and registered in the DKR over an interval corresponding to a 2-year inclusion period between July 1, 2011 and June 30, 2013 were identified. As index procedures in the final analysis, we chose only to include partial revisions (open debridement and exchange of tibial insert) and 2-stage exchange procedures (prosthesis removal and insertion of an antibiotic-releasing cemented spacer, and later, removal of the spacer and secondary insertion of a revision knee). It was a criterion for inclusion of a patient that the first stage of the 2-stage procedure had been performed within the inclusion period. The second-stage procedures that followed were also identified from the DKR, or from the Danish National Patient Register (DNPR) (Andersen et al. 1999, Lyngge et al. 2011) if performed after the inclusion period, with an end of follow-up at August 31, 2015 at the latest. (Figure 1).

Data were registered in the DKR by the orthopedic surgeons who performed the knee arthroplasty procedures. The DKR defined a revision procedure as a new operation in a previously resurfaced knee in which one or more of the components were exchanged, removed, or added. Thus, open debridement procedures without exchange of the tibial insert in prostheses with a non-modular tibial insert are not registered in the DKR. According to the DKR annual reports for 2012 and 2013 (DKR 2012, DKR 2013), 12% of all pri-

mary TKAs were non-modular types, and infections in the prosthesis treated with open debridement could not be covered in this study. The capture rate of revision procedures in the DKR was estimated to be 95% in 2013 (DKR 2013), based on data from the DNPR. The DNPR registers all hospitalizations, including diagnoses and surgical procedures at any Danish hospital. Reporting is mandatory for reimbursement of the hospital departments, which leads to a high degree of completeness of data registration (~99.4%) in the DNPR (Andersen et al. 1999, Lyngge et al. 2011). Neither the DNPR nor the DKR collect data on preoperative morbidity of patients, so this information was not available to us in the present study.

Outcome parameters

Failure after index revision surgery was defined as death within 90 days postoperatively, re-revision of the same knee due to infection, or not having reached second-stage surgery within the follow-up period for the 2-stage procedures.

Data on mortality were obtained through the Central Office of Civil Registration (CPR), which is based on the unique personal identification number given to all residents. The medical records of patients who died within 90 days of surgery were investigated to determine the cause of death.

Re-revisions due to infection were identified from the DKR and the DNPR, including examination of surgical notes, which ensured that we had complete data on re-revisions within the follow-up period. For the 2-stage procedures, we analyzed re-revisions due to infection and mortality after both the first and second stages. The patients who died and those who were re-revised due to infection were censored. End of follow-up was August 31, 2015 and the median follow-up time was 3.2 (2.2–4.2) years for the patients who were not censored.

Length of hospital stay (LOS) was defined as the number of postoperative nights in hospital (including transfer to other departments) until discharge to home, as rehabilitation units are not generally available in Denmark. For the 2-stage procedures, the cumulative LOS values from hospital admissions for both first- and second-stage surgery are presented. Information on LOS was obtained from the DNPR.

Statistics

Continuous data were tested for normal distribution using histograms. Medians with ranges are reported for skewed data, means with standard deviations (SDs) are reported for normally distributed data, and proportions are expressed as percentages with 95% confidence intervals (CIs). Normally distributed data were compared using independent-samples Student's *t*-test, and for skewed data the Mann-Whitney *U*-test was used. Proportions were compared using the Pearson chi-squared test, except when comparing mortality rates—where Fisher's exact test was used. Any *p*-value of 0.05 or less was considered to be statistically significant. Statistical analyses were done using SPSS version 20).

Table 1. Surgical subgroups, demographics, and related outcomes

	Partial revision	2-stage revision
Procedures	105	215
Patients	100	205
Mean age (SD)	70 (9.8)	69 (10)
Female, n (%)	49 (47)	85 (40)
Mean BMI (SD) ^a	30 (6.0)	29 (5.0)
First-time revision of a primary prosthesis, n (%) ^b	73 (70)	117 (54)
Outcome parameters		
Re-revision due to infection (%) (95% CI)	42 (40) (31–50)	52 (24) (19–30)
90-day mortality (%) (95% CI)	3 (3) (1–8)	10 (5) (3–8)
Median total LOS (range) ^c	18 (2–201)	24 (5–268)
Time course		
Median time from previous procedure, days (range) ^d	34 (10–6,325)	349 (10–5,463)
Median time from first to second stage, days (range)	-	84 (9–597)
Median time to re-revision due to infection, days (range)	138 (11–1,306)	95 (5–1,004)

^a Missing data in 36 cases.
^b Missing data in 3 cases.
^c For 2-stage procedures, accumulated LOS is given. The very short LOS in a few patients was due to early postoperative mortality.
^d Missing data in 21 cases.

Ethics

As this study was non-interventional, no ethical approval was required. Permission was obtained from the Danish Data Protection Agency (entry no. 2007-58-0015) and the Danish National Board of Health (3-3013-1302/1) to request and store medical records for analysis of postoperative complications.

Results

Partial revisions (open debridement and exchange of tibial insert)

The 105 partial revisions were performed in 100 patients (5 patients were operated twice: 2 were bilateral and 3 were operated twice in the same knee). In 71 cases (67%), the partial revision was a first-time revision of a primary prosthesis. The re-revision rate due to infection was 34% (CI: 24–46) in revisions of a primary prosthesis and it was 55% (CI: 38–71) in revisions of a previously revised prosthesis ($p = 0.05$).

In 42 cases (40%), a re-revision due to infection was performed within the follow-up period (Table 1). 3 patients (3%) died within 90 days of the partial revision procedure (Table 2). Hence, the failure rate of the partial revision procedure was 43% (Figure 2).

2-stage procedures

There were 215 cases of potential 2-stage procedures in 205 patients. 2 patients underwent three 2-stage procedures (in the

Table 2. Causes of mortality within 90 days postoperatively

Cause of death	Age	Surgical procedure ^a	Days postop.	Comment
Infection (n = 7)				
	89	2	1	Sepsis, multiple organ failure
	65	2	5	Sepsis, endocarditis, and stroke (cerebral embolism)
	86	1	6	Sepsis, endocarditis, and multiple organ failure
	80	2	16	Sepsis, treatment failure despite femoral amputation
	86	2	46	Sepsis, treatment failure, <i>Clostridium difficile</i> infection, and renal failure
	86	2	58	Sepsis, <i>Clostridium difficile</i> infection, and renal failure
	75	2	75	Sepsis, <i>Clostridium difficile</i> infection; no further treatment at patient's request
Cardiac (n = 3)				
	73	1	6	Unexpected cardiac arrest, failed resuscitation, no autopsy
	83	2	15	Cardiac failure; no intensive care treatment at patient's request
	75	1	77	Acute myocardial infarction, confirmed by autopsy
Pulmonary (n = 2)				
	91	2	2	Aspiration pneumonia
	77	2	40	Bilateral pneumonia, bacteremia
Gastrointestinal (n = 1)				
	91	2	23	Ileus; no treatment at patient's request

^a 1 means partial revision and 2 means 2-stage revision.

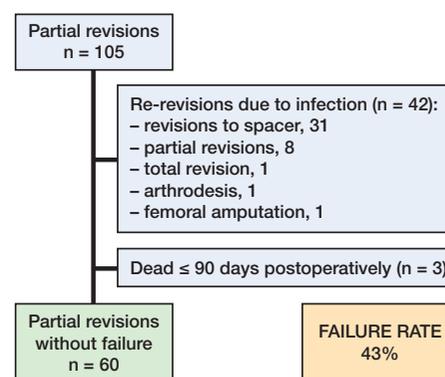


Figure 2. Results of the partial revisions.

first case all on the same knee, and in the other case twice on the left knee and once on the right knee). 6 patients underwent a 2-stage procedure twice on the same knee. 117 (54%) of the 2-stage revisions were first-time revisions of a primary prosthesis. The re-revision rate due to infection was 21% (CI: 14–29) in revisions of a primary prosthesis, as opposed to 29% (CI: 21–39) in revisions of a previously revised prosthesis ($p = 0.1$).

52 knees (24%) were re-revised due to infection after either first- or second-stage surgery within the follow-up period (Table 1). 10 patients (5%) died within 90 days of first- or

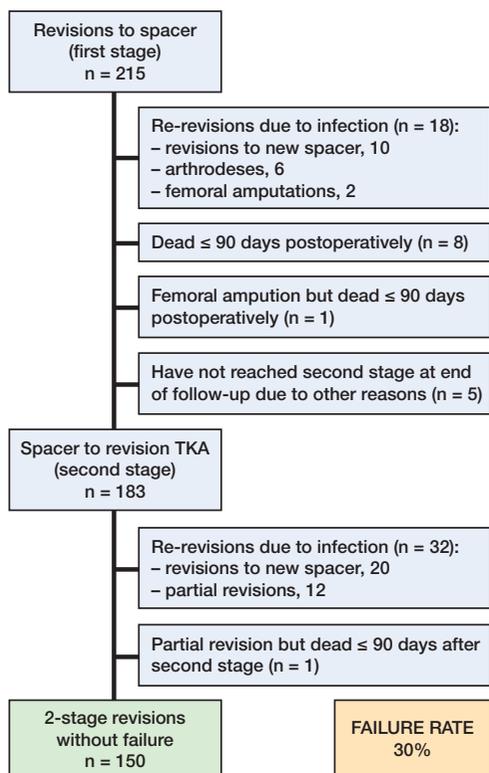


Figure 3. Results of the 2-stage procedures.

second-stage surgery (Table 2). Second-stage surgery was not reached within the follow-up period because of chronic septic arthritis in the affected knee and in several joints in 2 cases, paraplegia in 1 case, and severe medical comorbidities in 2 cases. These cases were considered to be failures. Thus, the failure rate of the 2-stage procedure was 30% (Figure 3).

The median time interval between the first stage and the second stage was 84 (9–597) days, and the re-revision rates due to infection were similar between cases revised within a time interval of < 90 days (18%, CI: 12–26) and cases revised within a longer time interval (20%, CI: 12–30) ($p = 0.7$).

Revision centers

25 centers performed the index infected revision knee arthroplasty procedures. 4 centers performed half of the procedures (57, 34, 33, and 31 procedures) in the 2-year study period. In contrast, 13 centers performed < 10 procedures each in the same period, representing one-fifth of the total number of procedures.

The re-revision rate due to infection was 28% (CI: 21–35) in the 4 high-volume centers, as compared to 31% (CI: 24–38) in the remaining centers ($p = 0.5$). The mortality rate of 0.6% (CI: 0.1–3.6) after surgery in high-volume centers was low compared to the 7% rate (CI: 4.2–12) found in the remaining centers ($p = 0.003$) (Table 3).

Table 3. Center volume and related outcomes

	High-volume centers ^a	Remaining centers	p-value
No. of centers	4	21	
Total procedures (%)	155 (48)	165 (52)	
Partial/2-stage revisions	50/105	55/110	
Mean age (SD)	70 (9.8)	69 (10.4)	0.1 ^b
Mean BMI (SD)	29 (5.1)	29 (5.6)	0.4 ^b
First-time revision of primary prosthesis (%)	84 (54)	106 (64)	0.06 ^c
Outcome parameters			
Re-revision due to infection (%) (95% CI)	43 (28) (21–35)	51 (31) (24–38)	0.5 ^d
90-day mortality (%) (95% CI)	1 (0.6) (0.1–3.6)	12 (7.3) (4.2–12)	0.003 ^e
Time course			
Median time from first to second stage, days (range) ^f	82 (9–343)	87 (42–597)	0.1 ^e

^a > 30 procedures in 2 years
^b t-test.
^c Pearson chi-squared test.
^d Fisher's exact test.
^e Mann-Whitney U-test.
^f Only 2-stage procedures.

Discussion

The main findings of this nationwide study were the high failure rates of 43% after the partial revision and 30% after the 2-stage revision procedure. These results confirm that surgical treatment of infected knee arthroplasties is a major challenge.

A 2-stage approach is—and has been—the gold standard in the treatment of infected total knee arthroplasties in the last 3 decades. Masters et al. (2013) reviewed the literature and found failure rates of a 2-stage approach to be < 20% in most previous studies, but higher failure rates, at the same level as the 30% found in our study, have been reported in 2 previous studies from the USA (Kurd et al. 2010, Mortazavi et al. 2011). The large differences in reported failure rates might be explained by differences in collecting data, length of follow-up, and definition of failure. We reported all first- and second-stage procedures as individual procedures, and not only the completed 2-stage procedures. In this way, we identified all the potential 2-stage procedures including those patients who failed and were re-revised after the first stage, died, or never reached the second stage for other reasons (Figure 3). Furthermore, we chose to include partial re-revisions that were performed due to infection and that did not reach the second stage within the follow-up period as failures, which may have led to a higher failure rate. On the other hand, we have no data on patients who were possibly chronically infected and who were not revised further, so the true failure rate may have been even higher. Importantly, most previous studies have been single-center investigations with results on 2-stage revisions from smaller cohorts with longer inclusion periods (Masters et al. 2013), so the results of our nationwide study may be more generalizable.

The median time interval of 84 days between first- and second-stage surgery in the present study indicates a strategy with 4–6 weeks of antibiotics, with subsequent cessation of antibiotics for 2–8 weeks prior to reimplantation, as recommended by experts in the USA (Osmon et al. 2013, Parvizi et al. 2013). We found similar re-revision rates due to infection in cases that were revised with a time interval between stages of less than or more than 90 days. An analysis of outcome between 2-stage procedures with a shorter interim period (e.g. 2–6 weeks and no cessation of antibiotics as recommended by Zimmerli and Ochsner (2003)) and 2-stage procedures with a longer interim period would have been interesting, but this was not possible in this study because very few cases were treated using a short interim period.

A 1-stage total revision approach for infected knee arthroplasty is rarely performed, and this was only used in 7 cases in our study. Considering the low success rate and the long interim period (median 84 days) of the 2-stage procedure, it might be time to use more 1-stage procedures in selected cases. Success rates of 90–100% have been reported after 1-stage approaches, but only in smaller feasibility studies (Buechel et al. 2004, Parkinson et al. 2011, Singer et al. 2012, Haddad et al. 2015) ($n = 22, 12, 63, 74$, respectively). If the safety and outcome of a 1-stage approach is at the same level as that of the 2-stage approach, there is much to gain from 1-stage surgery: i.e. shorter LOS and only 1 rehabilitation period. Drawbacks of the 1-stage approach might be an increased risk of biofilm formation and reinfection if surgical debridement and antibiotic treatment are insufficient (Gbejuade et al. 2015).

An implant salvage procedure with open debridement and polyethylene liner exchange (partial revision) is a tempting alternative to the more extensive and resource-intensive 1-stage and 2-stage prosthesis exchange procedures. However, high failure rates of 56–64% have been reported from the USA after this procedure (Azzam et al. 2010, Gardner et al. 2011, Odum et al. 2011, Fehring et al. 2013). In contrast, a recent Swedish nationwide study (Holmberg et al. 2015) ($n = 145$) found a failure rate of 25%, which is also lower than our findings of 43%. The Swedish study only included first-time revisions and did not consider re-revision with a new partial revision procedure as a failure if infection was later healed, which might explain some of the difference in failure rates reported in the 2 studies. The median time interval of 1 (0.3–211) month from the previous procedure in the same knee to the index partial revision in our study confirms that this procedure was mainly performed in early postoperative infections. Thus, the wide range shows that this procedure was also performed in acute hematogenous infections, and perhaps also in chronic infections. Wide indications for a partial revision in fragile patients who may not be considered to be fit to undergo more extensive 2-stage strategy may partially explain the high failure rate. However, this could not be confirmed or affirmed in this study without having detailed comorbidity data.

We have provided a detailed analysis of mortality within 90 days postoperatively (Table 2). The mortality rates of 3% and 5% after partial revision and 2-stage infected knee revision procedures are high compared to the rate of only 0.2% after aseptic revision knee surgery in Denmark (Lindberg-Larsen et al. 2014). The mortality was lower in the high-volume centers than in the remaining centers, but several different kinds of bias may have influenced these findings; and importantly, we were not able to describe potential differences in preoperative comorbidities. Our analysis showed that sepsis was the main cause of death after failed treatment. Furthermore, all remaining deaths were potentially related to infection or surgical trauma—and the patients who died were mainly elderly. These findings confirm the severity of periprosthetic joint infection, especially in the elderly. The high mortality overall may also reflect that the most vulnerable patients are more likely to be infected, but this could not be confirmed in this study without comorbidity data.

The high-volume centers in our study are referral centers that are expected to treat the most difficult cases in the most vulnerable patients, but despite this, the mortality was significantly lower in these centers. Revision knee surgery in the infected TKA is difficult, and high-risk procedures are performed on fragile patients. This puts heavy demands on surgical expertise and requires a high level of interdisciplinary perioperative collaboration between orthopedic surgeons, microbiologists, and anesthesiologists. However, such a perioperative setup may not be possible all centers. Our findings support future concentration of these operations to fewer centers.

The lack of information about the preoperative comorbidity and clinical scores of the patients was a limitation of this nationwide registry study. Unfortunately, this information is not reliably registered in the DNPR (Mason et al. 2012) or in the DKR (DKR 2013). Another limitation was the lack of information about microbiological agents and antibiotic therapy. We chose not to include microbiological data in this study, as the main aim was to determine early failure rates and mortality rates associated with revision procedures performed on the indication “infection”. However, information on the potential influence of the infecting microorganism and patient comorbidities on outcome are important, and they should be the subject of future research. This information is also necessary in order to determine selection criteria for a 1-stage approach in the treatment of the chronic infected knee arthroplasty. We acknowledge that some revision procedures performed on indications other than infection actually turn out to be infected, with positive intraoperative cultures (“silent” infections). The outcome of these procedures is not described in this study, as revision procedures performed for indications other than infection were not part of the inclusion criteria. Infectious revision hip arthroplasty procedures have been under-reported in the Danish Hip Arthroplasty Register (Gundtoft et al. 2015), and this might also be the case in the DKR. Whether or not under-reporting of infectious revi-

sions in the DKR would have biased our results is not known. However, we wanted to determine outcome and not the incidence of revision knee arthroplasty procedures performed due to infection, and we used combined registry data (DKR and DNPR) in the analysis in order not to underestimate failure rates (Witsø 2015). Information about spacer type (static or articulating) was not reliably registered in the DKR, and could not be addressed in this study. Finally, the relatively short follow-up period of median 3.2 years may have been a limitation. The failure rates might have been even higher with a longer follow-up period, but the high failure rates found despite the short follow-up period highlight the challenges involved in infectious revision knee surgery. However, the vast majority of failures should have been captured with the minimum follow-up of 2.2 years.

In summary, the results from this nationwide study confirm that revision surgery for prosthetic knee infection is a major challenge. The high failure rates of 43% after the partial revision procedure and 30% after the 2-stage revision procedure in combination with the higher mortality outside high-volume centers call for centralization and reconsideration of surgical strategies.

MLL, JB, HS, and HK designed the study. The data were collected and analyzed by MLL with support from CJ. MLL prepared the manuscript, which was edited by all the authors.

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No competing interests declared.

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