

Anti-rheumatic treatment and prosthetic joint infection: An observational study in 494 elective hip and knee arthroplasties.

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Abstract

Background Surgical site infections are more frequent among patients with rheumatic disease. To which extent this is related to immunosuppressive antirheumatic drugs is unclear, as is the value of discontinuing medication perioperatively.

Objectives To assess the rate of surgical site infections after knee and hip-replacement in patients with inflammatory joint disease, with emphasis on periprosthetic joint infection, and to investigate the importance of medical treatment in this regard.

Methods Data was collected from 494 primary elective hip- (51.4%) and knee arthroplasties along with demographic and medication data and primary outcome was surgical site infections during the first year after surgery.

Results In 78% (n=385) of the cases the patient medicated with 1 to 3 disease-modifying antirheumatic drugs perioperatively. Thirty two per cent (n=157) of patients were on a TNF-alpha inhibitor perioperatively. The rate of surgical site infections was 3.8% (n=19) The rate of periprosthetic joint infection was 1.4% (n=7), all of which were knee arthroplasties. Only in 1 case of periprosthetic joint infection the patient medicated perioperatively with a TNF-alpha inhibitor.

Conclusion Surgical site infections was not associated with ongoing medication with disease-modifying antirheumatic drugs. Due to low event rate this should be interpreted with caution. Routines at our centre, not stopping biologic disease-modifying antirheumatic drugs perioperatively, will be unchanged.

Introduction

In most affluent countries, treatment with biologic disease modifying drugs (bDMARD) such as TNF-alpha inhibitors, has during the past 20 years become part of standard of care for patients with rheumatoid arthritis (RA) as well as in other types of inflammatory joint disease, although the need for joint arthroplasty in these patients has decreased(1–7). There is still a number of patients in need of orthopedic surgery, and many of these patients are prior to the operation on treatment with conventional disease modifying drugs (cDMARDs) and/or bDMARDs.

The incidence of infections in general is higher in patients with RA than in non-RA subjects. If this is a consequence of immunologic disturbances due to the disease itself as disease severity is a risk factor for infection, or of the immunosuppressive treatment often used, or both, is still not fully understood.

TNF-alpha inhibitors are thought to increase the general risk of infection(8,9).

Studies vary in their findings regarding the risk of postoperative infections in patients on TNF-alpha inhibitors versus cDMARDs, such as methotrexate (Table 1). Prior studies suggest that methotrexate is not a substantial risk factor for surgical site infection (SSI)(10,11).

Table 1
studies on the influence of biologic DMARDS on SSI rate

Author, year	Type of surgery	Number of operations	bDMARD	Main finding in patients not stopping bDMARDs
Bibbo & Goldberg, 2004(45)	Foot and ankle surgery	31	continued treatment perioperatively	SSI ³ rate decreased
Talwalkar, Grennan, Gray, Johnson, & Hayton 2005(46)	Various orthopedic surgeries	11	TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively	SSI ³ rate unchanged
Wendling et al., 2005(47)	Various orthopedic surgeries	50	TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively	SSI ³ rate unchanged
Giles et al., 2006(48)	Various orthopedic surgeries	91	continued treatment perioperatively	SSI ³ rate increased
Broeder et al., 2007(49)	Various orthopedic surgeries	1 219	TNF-inhibitors discontinued 4 t1/2 prior to surgery or continued treatment perioperatively	SSI ³ rate unchanged
Ruysen-Witrand et al., 2007(50)	Various surgeries	127	variable timing for discontinuation prior to surgery	SSI ³ rate unchanged
Gilson et al., 2010(51)	Total joint replacement	60	cases treated with TNF-inhibitors included	SSI ³ rate increased
Kawakami et al., 2010(52)	Various orthopedic surgeries	128	TNF-inhibitors discontinued 2–4 weeks prior to surgery and restarted if no signs of infection	SSI ³ rate increased
Suzuki et al., 2011(53)	Arthroplasties	1 626	continued treatment perioperatively	SSI ³ rate increased
Momahara et al., 2011(54)	THA ¹ and TKA ²	420	TNF-inhibitors discontinued 2–4 weeks prior to surgery, cDMARDS continued	SSI ³ rate increased
Berthold et al., 2013(55)	Various orthopedic- and hand surgeries	1 596	TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively	SSI ³ rate increased
Tada et al., 2016(56)	Various orthopedic surgeries	332	TNF-inhibitors discontinued 2–4 weeks prior to surgery, cDMARDS continued	SSI ³ rate unchanged
Hayashi et al., 2017(57)	THA ¹	99	variable timing for discontinuation or not discontinuation prior to surgery	late SSI ³ rate increased
Salt et al., 2017(58)	THA ¹ , TKA ² and total shoulder arthroplasty	2 212	variable timing for discontinuation or not discontinuation prior to surgery	SSI ³ rate unchanged

¹ Total hip- arthroplasty, ²Total knee-arthroplasty, ³Surgical site infection

SSI, and specifically periprosthetic joint infection (PJI), is one of the most serious complications of arthroplasty and a leading cause of early revision (12,13). Risk factors for SSI include smoking, diabetes mellitus, obesity, ASA scale > 2("American Society of Anesthesiologists (ASA) Physical Status"), current infection and use of steroids(14–18). Rheumatic disease has been shown to be an independent risk factor for PJI(19–22).

In 2017, the American College of Rheumatology (ACR), published guidelines for the perioperative management of anti-rheumatic medication in patients with rheumatic diseases undergoing elective total hip and total knee arthroplasty. According to these recommendations, TNF-alpha inhibitors should be withheld prior to surgery and surgery planned for at the end of the dosing cycle(23).

The International Consensus Meeting (ICM) on orthopaedic infections, in Philadelphia 2018, adopted the ACR guidelines and estimated the level of evidence as moderate (24). Even the Swedish association for rheumatology has recommendations which are consistent with the ACR guidelines(25).

Guidelines on the prevention of SSI from the World Health organization, WHO, states that perioperative discontinuation of methotrexate has no effect on the risk of SSI, and perioperative discontinuation of TNF-alpha inhibitors might have a benefit in reducing the SSI rate. The evidence for this is however considered of very low quality and it is stated that "considering the scarce (or absent) evidence to support discontinuation of treatment (anti-TNF) and even potential harm it may cause (methotrexate) such as the risk of flare-up of the underlying disease(s) associated with the suspension of therapy, immunosuppressive medication should not be discontinued to prevent SSI"(26).

Since 2000 orthopedic surgery has been conducted at our departments of Orthopedics and Rheumatology Skåne University Hospital in Lund, Sweden, without interrupting methotrexate treatment. In 2006, new local guidelines were introduced and discontinuation of TNF-alpha inhibitors perioperatively in conjunction with rheumatic orthopedic surgery was abolished. Data from a study conducted at our departments from 2003 to 2009 did not indicate that the perioperative use of TNF-alpha inhibitors or methotrexate was a clinically important risk factor for PJI(27).

The aim of the present study was to answer two questions: (i) What is the one year incidence of SSI and PJI after total knee arthroplasty (TKA) and total hip arthroplasty (THA) in patients with inflammatory joint disease; and (ii) is there an association between the use of DMARDs and infection rate?

Methods

This is an observational, non- randomized retrospective single center study, using patient data from the departments of Rheumatology and Orthopedics at Skåne University Hospital, Lund, Sweden. The study was approved by the local ethics committee in Lund (Dnr 2016/880).

All adult patients above the age of 18 with rheumatic disease operated with primary TKA or THA between 2006 and 2015 were included in the study. Some patients had undergone more than one operation; the data analysis is based on cases (operations), not patients.

Information was collected from the local operation register. We included patients with an ICD 9 code for rheumatic disease: M058 or M059 (seropositive rheumatoid arthritis), M060 (seronegative rheumatoid arthritis), M069 (other rheumatoid arthritis), M073 (psoriatic and enteropathic arthropathies) or M080 (juvenile arthritis), who had undergone TKA or THA between January 2006 and December 2015. The diagnosis was validated by crosschecking the medical records. If the patient in conjunction with other surgery had been given an ICD 9 code for inflammatory joint disease,

and the diagnosis could be validated, the patient entered the study, even if he or she at the time of primary TKA or THA had been given a different diagnosis by the operating surgeon (most often osteoarthritis).

Postoperative infections are generally classified according to the US Center for Disease Control and Prevention (CDC) 1992 definition of nosocomial SSIs (28), where infections are divided into (i) superficial incisional SSI- involving the skin and subcutaneous tissue, (ii) deep incisional SSI- involving deep soft tissue of the incision and (iii) organ/space SSI- involving any part of the anatomy (e.g., organs or spaces), other than the incision, opened and manipulated during the operative procedure. In this study we used a modified definition of SSIs, according to what is generally used in the field of orthopedics, where "deep incisional SSI" and "organ/space SSI" together are referred to as PJI and superficial incisional SSI is termed superficial SSI.

For the diagnosis of PJI at least one of the following criteria was required for the diagnosis of PJI: (i) growth of identical microorganisms in at least two intraoperative cultures or a combination of preoperative aspiration and intraoperative cultures (ii) presence of a sinus tract communicating with the prosthetic joint, (iii) presence of purulence without another known etiology surrounding the prosthetic device(29).

By definition, superficial SSI occurs within 30 days after surgery and PJI within 1 year. Patients were followed for one year after surgery, or until death or re-operation for other reason than infection within one year. With a longer follow up time, one would expect to find a number of hematogenous infections, which was not our objective as these can not be related to medical treatment during the perioperative period. Routinely, patients were contacted by a nurse one year after the operation and asked for postoperative complications such as infections. In 8 cases, data regarding one year follow up was missing, and the patients' medical records were scrutinized for medical contacts which could indicate a SSI.

Statistics

The association between infectious rate and medication was analyzed using chi- square test or Fisher's exact test when appropriate, using SPSS Statistics 23 for Windows. The significance level was set at $p < 0.05$.

Results

A search in the local operation register provided 522 operations under the study period. Twenty-eight operations in 24 patients were excluded from further analysis. 5 patients had been diagnosed with polymyalgia rheumatica, 10 with osteoarthritis, 1 with calcium pyrophosphate arthritis, 1 with spondyloepiphyseal dysplasia, and in 7 cases data regarding rheumatic diagnosis could not be found. After exclusions, data was collected from 494 operations in 395 individual patients (Fig. 1). 92 patients had undergone more than one operation.

Patient characteristics are described in Table 2. A majority of cases were female (76%) and the mean age by time of surgery was 62 years (range 18–89). TKA comprised 51% of procedures (n = 245). A majority of cases had RA (69%) followed by juvenile idiopathic arthritis (JIA) (12%). The most used DMARD was methotrexate (55,5%), followed by a TNF-alpha inhibitor (31.8%). 18.2% of patients were on both methotrexate and a TNF- alpha inhibitor. Details on treatment is summarized in Table 3.

Table 2
Patients characteristics. Values are number (percentage) unless otherwise indicated.

All	494
Female	377 (76.3)
TKA ¹	254 (51.4)
THA ²	240 (48.6)
Age, years, by time of surgery, mean (range)	62.4 (18–89)
ASA ³ , valid no 451	
ASA 1	9 (2)
ASA 2	268 (59.4)
ASA 3	172 (38.1)
ASA 4	2 (0.4)
BMI ⁴ , kg/m ² , valid no 474, mean(range)	26.5(14.9–44.6)
Diagnosis	
Rheumatoid arthritis ^a	341 (69)
Psoriatic arthritis	35 (7)
Spondyloarthritis incl. ankylosing spondylitis ^b	29 (5.9)
Juvenile idiopathic arthritis ^c	59 (11.9)
Other diagnosis ^d	30 (6.1)

¹ Total knee-arthroplasty, ²Total hip-arthroplasty, ³American Society of Anesthesiologists (ASA) Physical Status, ⁴Body mass index

^a Seropositive rheumatoid arthritis (n = 283), seronegative rheumatoid arthritis (n = 58)

^b Ankylosing spondylitis (n = 21), other specified inflammatory spondylopathies (n = 6), inflammatory spondylopathy, unspecified (n = 2)

^c juvenile arthritis (n = 40), juvenile arthritis with systemic onset (n = 7), juvenile polyarthritis (seronegative) (n = 6), juvenile arthritis, unspecified (n = 4), pauciarticular juvenile rheumatoid arthritis (n = 2)

^d Inflammatory polyarthropathy (n = 1), polyarthritis, unspecified (n = 4), other specified arthritis (n = 4), monoarthritis, not elsewhere classified (n = 2), systemic lupus erythematosus, unspecified (n = 5), systemic lupus erythematosus with organ or system involvement (n = 3), adult-onset Still disease (n = 2), Crohn´s disease (n = 1), ulcerative colitis (n = 1), polymyositis (n = 1), systemic sclerosis (n = 2), other overlap syndrome (n = 1), arthritis unspecified (n = 1), systemic involvement of connective tissue, unspecified (n = 2)

Table 3

Exposure. Values are number (percentage) unless otherwise indicated.

Prednisolone	214 (43.3)
Prednisolone, dose mg/d, mean (valid no 489)	5.5
Number of ongoing DMARDs ¹	
0	109 (22.1)
1	243 (49.2)
2	132 (26.7)
3	10 (2)
cDMARD ²	343 (69.4)
Methotrexate	274 (55.5)
Methotrexate dose, mg/w, mean (valid no 488)	16
cDMARD ² other than methotrexate ^a	69 (14)
bDMARD ³	193 (39.1)
TNF- alpha inhibitor ^b	157 (31.8)
bDMARD ³ , other than TNF- alpha inhibitor ^c	36 (7.3)
Methotrexate and prednisolone	124 (25.1)
Methotrexate and TNF- alpha inhibitor	90 (18.2)
Methotrexate and prednisolone and TNF- alpha inhibitor	40 (8.1)

¹ Disease-modifying antirheumatic drug

² Conventional disease-modifying antirheumatic drug

³ Biologic disease-modifying antirheumatic drug

^a azathioprine (n = 9), sulfasalazine (n = 30), hydroxychloroquine (n = 26), mycophenolate mofetil (n = 3) and leflunomide (n = 1)

^b etanercept (n = 93), golimumab (n = 5), certolizumab (n = 12), infliximab (n = 15), adalimumab (n = 32)

^c abatacept (n = 6), rituximab (n = 16), anakinra (n = 5), tocilizumab (n = 14) One patient did bilateral THA at the same session and was treated with both anakinra and rituximab

The total incidence of SSI was 3.8% (n = 19). Of these, 12 were superficial SSI; the rate of superficial SSI being 2.4%. All of these healed after wound debridement and/or antibiotic treatment.

There were seven PJI; the one-year rate of PJI being 1.4%. All PJI occurred after TKA and there was a statistically significant difference in the rate of PJI depending on operating site (p = 0.015). One of the patients suffering a PJI had a

hematogenous infection 11 months after surgery, but is according to the design of the study counted as a SSI .

One patient with PJI was treated with the TNF-alpha inhibitor etanercept, and 4 patients were treated with methotrexate. There was no statistically significant difference in the rate of infection between patients treated with a TNF-alpha inhibitor and those not, ($p = 0.44$) or those treated with methotrexate ($p = 1.00$). No association could be found between PJI and prednisolone ($p = 0.25$), combination of TNF-alpha inhibitor and methotrexate ($p = 1.0$), combination of methotrexate and prednisolone ($p = 1.0$), combination of TNF-alpha inhibitor, methotrexate and prednisolone ($p = 1.0$), BMI ($p = 0.21$) or ASA-score ($p = 0.44$) (Table 4).

Table 4
Periprosthetic joint infection(PJI) and total surgical site infections(SSI) in various subgroups.

	total(n)	PJI(n)	p-value	total SSI (n)	p-value
Female	377	3		14	
Male	117	4	0.06 ^a	5	0.78 ^b
Procedure					
TKA ¹	254	7		11	
THA ²	240	0	0.015 ^a	8	0.33 ^b
BMI ³ , valid no 474					
< 30	368	4		12	
≥ 30	106	3	0.19 ^a	7	0.16 ^b
ASA ⁴ , valid no 448					
≤ 2	277	3		10	
≥ 3	174	4	0.44 ^a	8	0.60 ^b
Treatment					
Methotrexate	274	4	1.0 ^a	12	0.49 ^b
TNF-alpha inhibitor	157	1	0.44 ^a	5	0.60 ^b
Prednisolone	214	5	0.25 ^a	10	0.40 ^b
Methotrexate and prednisolone	124	2	1.00 ^a	4	0.79 ^a
Methotrexate and TNF-inhibitor	90	1	1.00 ^a	3	1.00 ^a
Methotrexate, TNF- inhibitor and prednisolone	39	0	1.00 ^a	0	0.39 ^a

¹ Total knee-arthroplasty, ²Total hip-arthroplasty, ³Body mass index ⁴American Society of Anesthesiologists (ASA) Physical Status.

^a Fisher´s exact test

^b Chi-square test

No correlation could be found between the total number of SSI and medical treatment (Table 4).

Five out of 7 PJI healed after treatment with debridement and antibiotics. Details on patients suffering PJI, including outcome are described in Table 5.

Table 5
, Periprosthetic joint infection (PJI), individual cases

Diagnosis	Age	Sex	Type of surgery	Anti-rheumatic treatment	Infectious agents	Treatment of PJI	Outcome
RA ¹ , seronegative	65	Female	TKA ³	Methotrexate, prednisolone	S. aureus	Debridement and exchange of tibial insert	Healed (26 months later re-infected with the same bacteria)
RA ¹ , seropositive	66	Male	TKA ³	Etanercept, methotrexate	coagulase negative staphylococcus (CNS)	Two-stage revision	Healed
RA ¹ , seropositive	70	Male	TKA ³	Prednisolone, azathioprine	S. aureus	Debridement and exchange of tibial insert	Failure (chronic infection treated with suppressive antibiotics)
RA ¹ , seropositive	69	Female	TKA ³	Methotrexate, prednisolone	B. fragilis	Antibiotics	Failure, amputation
RA ¹ , seropositive	66	Female	TKA ³	Methotrexate, sulfasalazine, hydroxychloroquine, prednisolone	S. mitis, S. hominis	Debridement and exchange of tibial insert	Healed
RA ¹ , seropositive	67	Male	TKA ³	Prednisolone	coagulase negative staphylococcus (CNS)	Debridement and exchange of tibial insert	Healed
PsA ²	44	Male	TKA ³	None	coagulase negative staphylococcus (CNS)	Debridement and exchange of tibial insert	Healed

¹ Rheumatoid arthritis, ²psoriatic arthritis.

- after consultation with a specialist in infectious diseases, all patients received treatment with antibiotics for a minimum of three months according to antimicrobial resistance pattern.

Four out of seven of patients with a PJI were male, although only 24% of the operations were performed on male patients. However, there was no statistically significant difference in the rate of PJI between men and women (p = 0.06) (Table 4).

Six patients died within one year of surgery. One patient died 20 days after surgery due to a gastrointestinal bleeding. Three patients died due to acute coronary syndrome, one due to a subarachnoid hemorrhage and one due to progressive dementia (Pick's disease). None of the deaths within one year of surgery could be linked directly to surgery or PJI.

Four patients underwent reoperation within one year from surgery. One patient was reoperated because of joint instability, two because of aseptic loosening of the prosthesis and one patient due to fracture after resurfacing hip arthroplasty.

Discussion

The main finding in this study is that no association could be found between ongoing treatment with bDMARD and PJI, or SSI in general, amongst patients with inflammatory joint disease undergoing primary knee or hip arthroplasty.

A previous study from our center(27) showed a increased risk of PJI in patients who continued treatment with TNF-alpha inhibitors perioperatively to hand and orthopedic surgery, however the finding was caused by a very low incidence rate of PJI in foot surgery in the comparison group.

A meta analysis comparing continuation versus discontinuation of TNF- alpha inhibitors prior to orthopedic surgery favors discontinuation of bDMARD(8) although the studies included are heterogeneous with different time of treatment interruption and a variety of patients and operations included. Further, the included studies were underpowered to detect small changes in infection rate.

As shown in Table 1. other studies on the influence of TNF-alpha inhibitors on infection rates comes to different conclusions. Eight studies showed a slight increase in PJI rate(9,11,19,30–34), whereas seven(17,35–40) showed no increase or a decrease in PJI in patients treated perioperatively with TNF-alpha inhibitors. The studies included different types of surgery, some compared patients not treated with TNF-alpha inhibitors too those treated with TNF-alpha inhibitors and some compared the result after continuation versus discontinuation of TNF- alpha inhibitors prior to surgery. Also the time of treatment interruption varied which makes conclusions difficult.

The rate of PJI after TKA was 2.8% which is a higher frequency compared to data from the Swedish Knee Arthroplasty Register (SKAR). Here, the one year incidence for revision due to infection is 1.7% for TKA performed 2006–2011(41). Most patients in SKAR have osteoarthritis, and patients with RA have previously been shown to have a increased risk for PJI compared to patients with osteoarthritis(42,43). A Norwegian study with data from The Norwegian Arthroplasty Register reports a one year revision rate of 1.2% in TKA performed in RA patients(43). In a Danish cohort the one year incidence rate in a population of RA patients for PJI in TKA and THA together the was 1.6%(42).

The rate of PJI was 1.4% which is comparable to what have been found in other studies on subjects with rheumatic disease(19,42).

None of the THA performed in our study resulted in a PJI. The Swedish Hip Arthroplasty Register (SHPR) reported an re-operation rate due to infection of 1.2% in THA performed in Sweden 2005–2008(44). The fact that the incidence rate of THA was lower than expected could be coincidental or be due to low number of procedures in this study although the same pattern with higher risk of revision in RA patients undergoing a TKA than a THA has been showed previously(43).

In only one of the seven cases of PJI the patient was treated with a TNF-alpha inhibitor, in this case etanercept. In all 157 (31.8%) of patients was treated with a TNF-alpha inhibitor which means that only 0.63% of patients treated with a TNF-alpha inhibitor suffered a PJI.

In 2003–2005, before the new policy of perioperative continuation of TNF-alpha inhibitors were introduced in our departments, only 0.6% of implant operations led to a PJI (27). Compared to this very low incidence rates the present finding of 1.4% is higher, but few cases and makes interpretation difficult.

One patient with PJI suffered a hematogenous infection with streptococcus mitis 11 months after surgery. The fact that the infection occurred long after surgery may suggest that the treatment at time of surgery was not a significant contributor to the infectious outcome. Leaving out this infection the rate of PJI would have been 1.2%.

Men were overrepresented in the group with PJI($p = 0.06$) which is consistent with previous findings(15–17).

PJI is a serious complication of arthroplasty and potential risk factors for infection should if possible be eliminated prior to surgery. With this in mind, the risk of flares in patients with rheumatic disease when discontinuing DMARD treatment should be carefully considered when deciding whether to continue or discontinue DMARD treatment prior to surgery. Although TNF-alpha inhibitors are not discontinued perioperatively to elective arthroplasty surgery at our center we do not apply this approach as a general rule for others DMARDs such as rituximab, tocilizumab or JAK inhibitors where data are scarcer.

This was a single center study, and procedures were performed by a few experienced surgeons according to the same routines throughout the study period. One year follow-up was standardized via a telephone call and data on perioperative medications were retrieved by one investigator (YB) via medical records. There were few missing data (Table 3), mostly regarding dosing of methotrexate and prednisolone, which do not effect the result.

The limitations of this study includes that it is observational and descriptive, not including a control group. The overall rate of SSI including PJI is low, and it is thus underpowered, like all other investigations in the field. From available data, Table 1, it seems likely that treatment with TNF- alpha inhibitors per se confers a somewhat increased risk of PJI. The importance of perioperative stopping the treatment is unclear. In fact, it is not likely that a randomized, controlled trial of stopping bDMARDs perioperatively will be performed, as this would require a very large number of procedures. Furthermore, each bDMARD would require its own trial. Assuming a general PJI incidence of 2%, a clinical trial would have to include 21,108 procedures within each group (continuation versus cessation of bDMARD perioperatively) to detect a 20% increase of PJI incidence with a power of 80%.

In conclusion, in our study we found no signs of increased PJI risk despite perioperative bDMARD treatment in inflammatory joint disease patients undergoing elective TKA or THA.

The policy at our center of perioperative continuation of most bDMARDs will be unchanged. More and larger studies are needed to elucidate the role, if any, of perioperative treatment cessation in reducing PJI rates.

References

1. Fevang BTS, Lie SA, Havelin LI, EngesÆter LB, Furnes O. Reduction in orthopedic surgery among patients with chronic inflammatory joint disease in Norway, 1994–2004. *Arthritis Care & Research*. [Online] 2007;57(3): 529–532. Available from: doi:10.1002/art.22628
2. Jämsen E, Virta LJ, Hakala M, Kauppi MJ, Malmivaara A, Lehto MUK. The decline in joint replacement surgery in rheumatoid arthritis is associated with a concomitant increase in the intensity of anti-rheumatic therapy. *Acta Orthopaedica*. [Online] 2013;84(4): 331–337. Available from: doi:10.3109/17453674.2013.810519

3. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983–2007. *Annals of the Rheumatic Diseases*. [Online] 2010;69(5): 868–871. Available from: doi:10.1136/ard.2009.112474
4. Nystad TW, Fenstad AM, Furnes O, Fevang BT. Predictors for orthopaedic surgery in patients with rheumatoid arthritis: results from a retrospective cohort study of 1010 patients diagnosed from 1972 to 2009 and followed up until 2015. *Scandinavian Journal of Rheumatology*. [Online] 2018;47(4): 282–290. Available from: doi:10.1080/03009742.2017.1397188
5. Skyttä ET, Honkanen PB, Eskelinen A, Huhtala H, Remes V. Fewer and older patients with rheumatoid arthritis need total knee replacement. *Scandinavian Journal of Rheumatology*. [Online] 2012;41(5): 345–349. Available from: doi:10.3109/03009742.2012.681061
6. Weiss RJ, Ehlin A, Montgomery SM, Wick MC, Stark A, Wretenberg P. Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: data from 54 579 Swedish RA inpatients. *Rheumatology*. [Online] 2008;47(4): 491–494. Available from: doi:10.1093/rheumatology/ken009
7. Cordtz RL, Hawley S, Prieto-Alhambra D, Højgaard P, Zobbe K, Overgaard S, et al. Incidence of hip and knee replacement in patients with rheumatoid arthritis following the introduction of biological DMARDs: an interrupted time-series analysis using nationwide Danish healthcare registers. *Annals of the Rheumatic Diseases*. [Online] 2018;77(5): 684–689. Available from: doi:10.1136/annrheumdis-2017-212424
8. Clay M, Mazouyes A, Gilson M, Gaudin P, Baillet A. Risk of postoperative infections and the discontinuation of TNF inhibitors in patients with rheumatoid arthritis: A meta-analysis. *Joint Bone Spine*. [Online] 2016;83(6): 701–705. Available from: doi:10.1016/j.jbspin.2015.10.019
9. Mabile C, Degboe Y, Constantin A, Barnetche T, Cantagrel A, Ruysse-Witrand A. Infectious risk associated to orthopaedic surgery for rheumatoid arthritis patients treated by anti-TNFalpha. *Joint, Bone, Spine: Revue Du Rhumatisme*. [Online] 2017;84(4): 441–445. Available from: doi:10.1016/j.jbspin.2016.06.011
10. Grennan DM. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Annals of the Rheumatic Diseases*. [Online] 2001;60(3): 214–217. Available from: doi:10.1136/ard.60.3.214
11. Momohara S, Kawakami K, Iwamoto T, Yano K, Sakuma Y, Hiroshima R, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. *Modern Rheumatology*. [Online] 2011;21(5): 469–475. Available from: doi:10.3109/s10165-011-0423-x
12. Dalury DF, Pomeroy DL, Gorab RS, Adams MJ. Why are total knee arthroplasties being revised? *The Journal of Arthroplasty*. [Online] 2013;28(8 Suppl): 120–121. Available from: doi:10.1016/j.arth.2013.04.051
13. Portillo ME, Salvadó M, Alier A, Sorli L, Martínez S, Horcajada JP, et al. Prosthesis Failure Within 2 Years of Implantation Is Highly Predictive of Infection. *Clinical Orthopaedics and Related Research*. [Online] 2013;471(11): 3672–3678. Available from: doi:10.1007/s11999-013-3200-7
14. Castano-Betancourt MC, Fruschein Annichino R, de Azevedo E Souza Munhoz M, Gomes Machado E, Lipay MV, Marchi E. Identification of high-risk groups for complication after arthroplasty: predictive value of patient's related risk factors. *Journal of Orthopaedic Surgery and Research*. [Online] 2018;13(1): 328. Available from: doi:10.1186/s13018-018-1036-2
15. Kong L, Cao J, Zhang Y, Ding W, Shen Y. Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis. *International Wound Journal*. [Online] 2017;14(3): 529–536. Available from: doi:10.1111/iwj.12640

16. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Patient-Related Risk Factors for Periprosthetic Joint Infection after Total Joint Arthroplasty: A Systematic Review and Meta-Analysis. *PloS One*. [Online] 2016;11(3): e0150866. Available from: doi:10.1371/journal.pone.0150866
17. Salt E, Wiggins AT, Rayens MK, Morris BJ, Mannino D, Hoellein A, et al. Moderating effects of immunosuppressive medications and risk factors for post-operative joint infection following total joint arthroplasty in patients with rheumatoid arthritis or osteoarthritis. *Seminars in Arthritis and Rheumatism*. [Online] 2017;46(4): 423–429. Available from: doi:10.1016/j.semarthrit.2016.08.011
18. Tande AJ, Patel R. Prosthetic Joint Infection. *Clinical Microbiology Reviews*. [Online] 2014;27(2): 302–345. Available from: doi:10.1128/CMR.00111-13
19. Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. *Arthritis and Rheumatism*. [Online] 2008;59(12): 1713–1720. Available from: doi:10.1002/art.24060
20. Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient-related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. *Clinical Orthopaedics and Related Research*. [Online] 2012;470(1): 130–137. Available from: doi:10.1007/s11999-011-2043-3
21. Jover-Saénz A, Barcenilla-Gaite F, Torres-Puig-Gros J, Prats-Gispert L, Garrido-Calvo S, Porcel-Pérez JM. [Risk factors for total prosthetic joint infection. Case-control study]. *Medicina Clinica*. 2007;128(13): 493–494.
22. Schrama JC, Fenstad AM, Dale H, Havelin L, Hallan G, Overgaard S, et al. Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements. *Acta Orthopaedica*. [Online] 2015;86(4): 469–476. Available from: doi:10.3109/17453674.2015.1017793
23. Goodman SM, Springer B, Guyatt G, Abdel MP, Dasa V, George M, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty: ACR/AAHKS Guideline for Perioperative Management. *Arthritis Care & Research*. [Online] 2017;69(8): 1111–1124. Available from: doi:10.1002/acr.23274
24. Iorio R, Cizmic Z, Feng James E, Kunutsor S. *Hip and Knee*. [Online] ICM Philly. Available from: <https://icmphilly.com/document/icm-2018-hip-and-knee-document/> [Accessed: 8th February 2019]
25. Baecklund E, Innala L, Wiberg K, Kapetanovic M, Kvarnström M, Larsson K. *Hantering av antireumatiska läkemedel vid elektiv reumakirurgi*. [Online] Svensk Reumatologisk Förening. Available from: <http://svenskeumatologi.se/srfs-riktlinjer/> [Accessed: 22nd September 2018]
26. Allegranzi B, Bischoff P, Kubilay Z, de Jonge S, Zayed B, Abbas M, et al. *WHO | Global guidelines on the prevention of surgical site infection*. [Online] WHO. Available from: <http://www.who.int/gpsc/ssi-prevention-guidelines/en/> [Accessed: 7th October 2018]
27. Berthold E, Geborek P, Gülfe A. Continuation of TNF blockade in patients with inflammatory rheumatic disease. An observational study on surgical site infections in 1,596 elective orthopedic and hand surgery procedures. *Acta Orthopaedica*. [Online] 2013;84(5): 495–501. Available from: doi:10.3109/17453674.2013.842431
28. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infection Control and Hospital Epidemiology*. 1992;13(10): 606–608.
29. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. [Online] 2013;56(1): e1–e25. Available from: doi:10.1093/cid/cis803

30. Suzuki M, Nishida K, Soen S, Oda H, Inoue H, Kaneko A, et al. Risk of postoperative complications in rheumatoid arthritis relevant to treatment with biologic agents: a report from the Committee on Arthritis of the Japanese Orthopaedic Association. *Journal of Orthopaedic Science: Official Journal of the Japanese Orthopaedic Association*. [Online] 2011;16(6): 778–784. Available from: doi:10.1007/s00776-011-0142-3
31. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. *Arthritis and Rheumatism*. [Online] 2006;55(2): 333–337. Available from: doi:10.1002/art.21841
32. Gilson M, Gossec L, Mariette X, Gherissi D, Guyot M-H, Berthelot J-M, et al. Risk factors for total joint arthroplasty infection in patients receiving tumor necrosis factor α -blockers: a case-control study. *Arthritis Research & Therapy*. [Online] 2010;12(4): R145. Available from: doi:10.1186/ar3087
33. Kawakami K, Ikari K, Kawamura K, Tsukahara S, Iwamoto T, Yano K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications? *Rheumatology (Oxford, England)*. [Online] 2010;49(2): 341–347. Available from: doi:10.1093/rheumatology/kep376
34. Hayashi S, Hashimoto S, Takayama K, Matsumoto T, Takebe K, Terashima Y, et al. Risk factors for late deep infection after total hip arthroplasty in patients with rheumatoid arthritis. *Acta Reumatologica Portuguesa*. 2017;42(2): 150–154.
35. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. *Foot & Ankle International*. [Online] 2004;25(5): 331–335. Available from: doi:10.1177/107110070402500510
36. Talwalkar SC, Grennan DM, Gray J, Johnson P, Hayton MJ. Tumour necrosis factor alpha antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery. *Annals of the Rheumatic Diseases*. [Online] 2005;64(4): 650–651. Available from: doi:10.1136/ard.2004.028365
37. Wendling D, Balblanc J-C, Brousse A, Lohse A, Lehuède G, Garbuio P, et al. Surgery in patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an observational study on 50 surgical procedures. *Annals of the Rheumatic Diseases*. [Online] 2005;64(9): 1378–1379. Available from: doi:10.1136/ard.2005.037762
38. Broeder AA den, Creemers MCW, Fransen J, Jong E de, Rooij D-JR de, Wymenga A, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *The Journal of Rheumatology*. 2007;34(4): 689–695.
39. Ruysse-Witrand A, Gossec L, Salliot C, Luc M, Duclos M, Guignard S, et al. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. *Clinical and Experimental Rheumatology*. 2007;25(3): 430–436.
40. Tada M, Inui K, Sugioka Y, Mamoto K, Okano T, Kinoshita T, et al. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. *Clinical Rheumatology*. [Online] 2016;35(6): 1475–1481. Available from: doi:10.1007/s10067-016-3274-1
41. Sundberg M, Lidgren L, W-Dahl A, Robertsson O. *Årsrapport 2013, Svenska knäprotesregistret*. [Online] Available from: http://www.myknee.se/pdf/SKAR2013_Sv1.1.pdf
42. Cordtz RL, Zobbe K, Højgaard P, Kristensen LE, Overgaard S, Odgaard A, et al. Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers. *Annals of the Rheumatic Diseases*. [Online] 2018;77(2): 281–288. Available from: doi:10.1136/annrheumdis-2017-212339

43. Schrama JC, Espehaug B, Hallan G, Engesæter LB, Furnes O, Havelin LI, et al. Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared with osteoarthritis: A prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register. *Arthritis Care & Research*. [Online] 2010;62(4): 473–479. Available from: doi:10.1002/acr.20036
44. Garellick G, Rogmark C, Kärrholm J, Rolfson O. *Swedish Hip Arthroplasty Register Annual Report 2012*. [Online] Available from: <https://registercentrum.blob.core.windows.net/shpr/r/Annual-report-2012-HJBqtLpig.pdf> [Accessed: 19th June 2019]
45. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. *Foot & Ankle International*. [Online] 2004;25(5): 331–335. Available from: doi:10.1177/107110070402500510
46. Talwalkar SC, Grennan DM, Gray J, Johnson P, Hayton MJ. Tumour necrosis factor alpha antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery. *Annals of the Rheumatic Diseases*. [Online] 2005;64(4): 650–651. Available from: doi:10.1136/ard.2004.028365
47. Wendling D, Balblanc J-C, Brousse A, Lohse A, Lehuède G, Garbuio P, et al. Surgery in patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an observational study on 50 surgical procedures. *Annals of the Rheumatic Diseases*. [Online] 2005;64(9): 1378–1379. Available from: doi:10.1136/ard.2005.037762
48. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. *Arthritis and Rheumatism*. [Online] 2006;55(2): 333–337. Available from: doi:10.1002/art.21841
49. Broeder AA den, Creemers MCW, Fransen J, Jong E de, Rooij D-JR de, Wymenga A, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *The Journal of Rheumatology*. 2007;34(4): 689–695.
50. Ruysse-Witrand A, Gossec L, Salliot C, Luc M, Duclos M, Guignard S, et al. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. *Clinical and Experimental Rheumatology*. 2007;25(3): 430–436.
51. Gilson M, Gossec L, Mariette X, Gherissi D, Guyot M-H, Berthelot J-M, et al. Risk factors for total joint arthroplasty infection in patients receiving tumor necrosis factor α -blockers: a case-control study. *Arthritis Research & Therapy*. [Online] 2010;12(4): R145. Available from: doi:10.1186/ar3087
52. Kawakami K, Ikari K, Kawamura K, Tsukahara S, Iwamoto T, Yano K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications? *Rheumatology (Oxford, England)*. [Online] 2010;49(2): 341–347. Available from: doi:10.1093/rheumatology/kep376
53. Suzuki M, Nishida K, Soen S, Oda H, Inoue H, Kaneko A, et al. Risk of postoperative complications in rheumatoid arthritis relevant to treatment with biologic agents: a report from the Committee on Arthritis of the Japanese Orthopaedic Association. *Journal of Orthopaedic Science: Official Journal of the Japanese Orthopaedic Association*. [Online] 2011;16(6): 778–784. Available from: doi:10.1007/s00776-011-0142-3
54. Momohara S, Kawakami K, Iwamoto T, Yano K, Sakuma Y, Hiroshima R, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. *Modern Rheumatology*. [Online] 2011;21(5): 469–475. Available from: doi:10.3109/s10165-011-0423-x

55. Berthold E, Geborek P, Gülfe A. Continuation of TNF blockade in patients with inflammatory rheumatic disease. An observational study on surgical site infections in 1,596 elective orthopedic and hand surgery procedures. *Acta Orthopaedica*. [Online] 2013;84(5): 495–501. Available from: doi:10.3109/17453674.2013.842431
56. Tada M, Inui K, Sugioka Y, Mamoto K, Okano T, Kinoshita T, et al. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. *Clinical Rheumatology*. [Online] 2016;35(6): 1475–1481. Available from: doi:10.1007/s10067-016-3274-1
57. Hayashi S, Hashimoto S, Takayama K, Matsumoto T, Takebe K, Terashima Y, et al. Risk factors for late deep infection after total hip arthroplasty in patients with rheumatoid arthritis. *Acta Reumatologica Portuguesa*. 2017;42(2): 150–154.
58. Salt E, Wiggins AT, Rayens MK, Morris BJ, Mannino D, Hoellein A, et al. Moderating effects of immunosuppressive medications and risk factors for post-operative joint infection following total joint arthroplasty in patients with rheumatoid arthritis or osteoarthritis. *Seminars in Arthritis and Rheumatism*. [Online] 2017;46(4): 423–429. Available from: doi:10.1016/j.semarthrit.2016.08.011

Abbreviations

ACR- American College of Rheumatology

ASA- American Society of Anesthesiologists (ASA) Physical Status

bDMARD- biologic disease-modifying antirheumatic drug

cDMARD- conventional disease-modifying antirheumatic drug

CNS- coagulase negative staphylococcus

ICD-9- International Statistical Classification of Disease

ICM- International Consensus Meeting

PJI- Periprosthetic joint infection

PsA- psoriatic arthritis

RA- rheumatoid arthritis

SHPR- Swedish Hip Arthroplasty Register

SKAR- Swedish Knee Arthroplasty Register

SRF- Svensk reumatologisk förening

SSI- surgical site infection

THA- total hip- arthroplasty

TKA- total knee- arthroplasty

TNF α - tumor necrosis factor alpha

Declarations

There are no competing interests for any author.

Data are available upon reasonable request.

This study is approved by the Local ethics committee in Lund (Dnr 2016/880).

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Figures

Fig. 1

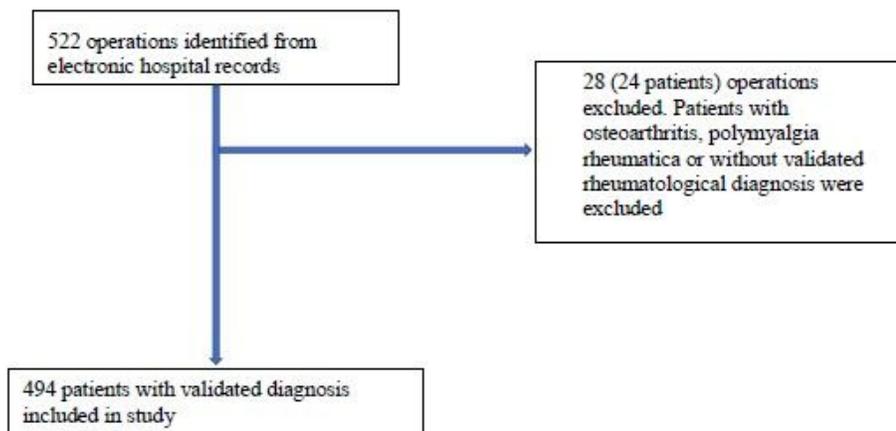


Figure 1

After exclusions, data was collected from 494 operations in 395 individual patients (Figure 1). 92 patients had undergone more than one operation.