Surgical interventions for nephrolithiasis in ankylosing spondylitis and the general population

Ane Krag Jakobsen1, L. T. H. Jacobsson2,3, O. Patschan1, T. Hopfgarten1, J. Askling4 and L. E. Kristensen3,5

1Department of Urology, Skåne University Hospital, Lund University, Malmö, Sweden, 2Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 3Department of Clinical Sciences, Section of Rheumatology, Lund University, Malmö, Sweden, 4Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine (Solna), Karolinska Institutet, Stockholm, Sweden, and 5The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Frederiksberg, Denmark

Abstract
Objective. The aim of this study was to estimate rates and type of definitive surgical interventions for nephrolithiasis in Swedish patients with ankylosing spondylitis (AS) compared to the general population. Materials and methods. This national prospective cohort study linked data from Swedish population and healthcare registries. Incidence rates and interventions for nephrolithiasis during follow-up in patients with AS were compared to general population comparator (GPC) subjects. Results. In total, 8572 AS patients were followed for 49,959 person-years and 39,639 matched GPCs were followed for 225,221 person-years. Mean age at study entry was 46 years (interquartile range [IQR] 36–56 years) and 65% were male. In AS patients with a diagnosis of nephrolithiasis during the study period, 29% (72/250) underwent similar intervention for nephrolithiasis compared to 24% (114/466) GPCs (p = 0.21). The incidence rate ratio (RR) in overall AS patients was 3.2 (95% CI 1.97–4.54) and in AS matched subjects was 2.9 (95% confidence interval (CI) 2.1–3.8) during a median follow-up of 6.2 years (IQR 3.2–8.6 years). With prior diagnosis of nephrolithiasis, the RR was 3.7 (95% CI 1.8–7.7); without prior nephrolithiasis the RR was 2.1 (95% CI 1.5–3.0). Increasing age (odds ratio (OR) 1.02, 95% CI 1.01–1.03), prior nephrolithiasis diagnosis (OR 3.3, 95% CI 1.97–5.62) and atherosclerotic cardiac disease (OR 2.0, 95% CI 1.03–3.91) were identified as predictors of intervention for nephrolithiasis. Conclusions. Patients with AS have an almost three-fold increased risk of surgical intervention for kidney stones, with similar management, compared to the general population.

Keywords: Ankylosing spondylitis, comparative study, lithotripsy, nephrolithiasis, percutaneous nephrolithotomy, ureteroscopy

Introduction
Nephrolithiasis, defined as a urinary stone in the upper urinary tract, poses a substantial and growing healthcare burden worldwide [1,2]. Nephrolithiasis is managed conservatively in selected cases. However, pharmacological and/or surgical intervention is frequently needed. The choice of treatment depends on the location and size of the stone, the degree of obstruction, and the patient’s comorbidities and symptoms. In addition, other factors related to the individual patient, to the treating physician and to the healthcare institution may influence how nephrolithiasis is managed [3–7].

During the past 30 years the surgical management of symptomatic upper urinary tract calculi has developed dramatically. Open lithotomy has now almost entirely been replaced by minimally invasive endoscopic and non-invasive techniques, including percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery, ureteroscopic procedures and extracorporeal shockwave lithotripsy (ESWL) [8–11].

In a recently published study, the present authors identified a more than two-fold risk of nephrolithiasis in Swedish patients with ankylosing spondylitis (AS) [12].

The aim of the present study is to describe the frequency of definitive interventions for nephrolithiasis and choice of treatment modality in AS patients compared to the general population in Sweden. To do this, a population-based prospective cohort design was used, with linkage of several national population and healthcare registers [13].

Materials and methods
This Swedish population- and register-based nationwide prospective cohort study used register data from 1 January 1997 to 31 December 2009, comparing AS patients to matched subjects in the general population.

Ethical approval for the study was granted by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden (ethical no. 2011/29-31/1). No informed consent was applicable as the study involved only register linkage, and no actual handling of patients.
Data sources

On 31 December 2009, Sweden had a population of approximately 9.2 million. Health and demographic information on all inhabitants is updated annually in a series of national registers, with a high degree of completeness [14]. Linkage of data from these registers is possible using the 10-digit personal identification number automatically assigned to all Swedish residents.

The Swedish healthcare system is tax funded and offers universal access. Data on healthcare contacts at inpatient (somatic, starting in 1964; psychiatric, starting in 1973) and non-primary outpatient (starting in 2001) facilities are registered in the Swedish Patient Register.

Available data include date of contact and diagnoses given by the treating physician according to the Swedish version of the International Statistical Classification of Diseases (ICD-10, starting in 1997) as well as codes on surgical procedures performed according to the Swedish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (KKÅ97) [15]. Reporting of data on each single healthcare contact, excluding primary care visits, is statutory.

The majority of patients with AS are diagnosed by rheumatologists at public outpatient and inpatient facilities. Patients with nephrolithiasis are also diagnosed and treated in both inpatient and outpatient settings, but by physicians from a wider variety of specialties including urologists, general surgeons, specialists in acute medicine, specialists in internal medicine and general practitioners. Surgical interventions for nephrolithiasis are exclusively performed within urological specialist care facilities, as both inpatient and outpatient procedures.

Study population

A prospective national population-based cohort of AS patients was identified using data from the Swedish Patient Register. Patients aged 16 years or older, who attended an outpatient clinic (Rheumatology or Internal Medicine Department) during the period 1 January 2001 to 31 December 2009 and who received at least one ICD code corresponding to AS (ICD-10: M459) were included. Patients with a previously or concomitantly registered diagnosis code of systemic lupus erythematosus (ICD-10: M32.0, M32.1, M32.8, M32.9) or juvenile inflammatory arthritis (ICD-10: M08-09) were excluded from the analyses.

The validity of the AS diagnosis in this cohort has been estimated to be approximately 90% [16].

Through register linkage, data on death, emigration and level of education (≤9 years, 10–12 years, >12 years) were retrieved from the Swedish Population Register, the Swedish Cause of Death Register and the Swedish Register of Education.

For each AS patient, up to five general population comparators (GPCs) were identified (from the Swedish Population Register) and matched on year of birth, gender and county. GPC subjects had to be alive and without AS by the time of the index patient’s first AS diagnosis during the study period. Ninety-three per cent of the AS patients had at least four controls.

Follow-up

Cases and matched GPC subjects contributed to “time-at-risk” from the time of study entry (1 January 2001 for those registered with AS diagnosis before or on that date, and from the date of AS diagnosis for those with their first AS diagnosis after 1 January 2001) until 31 December 2009, death, emigration or the first occurrence of nephrolithiasis intervention during follow-up, whichever came first. Figure 1 illustrates inclusion, exclusion, censoring and losses to follow-up of AS patients and GPCs before and during the study period.

Primary and secondary outcomes

Data on nephrolithiasis diagnosis (ICD-10: N20, N23.9) and interventions for nephrolithiasis registered by physicians in hospital-based inpatient or outpatient somatic care clinics in AS patients and GPC subjects, before study entry (1 January 1997 to 31 December 2000) and during follow-up (1 January 2001 to 31 December 2009), were retrieved from the Swedish Patient Register.

The primary outcome of this study was defined as the first registered KKÅ97 code corresponding to a definitive intervention for nephrolithiasis during follow-up, regardless of any interventions for nephrolithiasis before follow-up. Definitive interventions for nephrolithiasis were defined as PCNL of pelvic and proximal ureteric stones (KAE11, KBE01, KAE97, KBE97), retrograde intrarenal surgery of pelvic stones (KAE12, KAE98), ureteroscopic procedures (KBE12,
KBE98), open surgery removing stones in the pelvis or ureter (KAE10, KAE96, KBE00, KBE96) and ESWL of stones in the pelvis or ureter (KAT00 or KBT00).

As a secondary outcome, the frequency of the different surgical modalities in AS and GPC during the study period was assessed. In addition, a surgical fraction, i.e. the fraction of AS and GPC with a registered nephrolithiasis diagnosis during the study period who underwent at least one definitive intervention for nephrolithiasis, was calculated.

Data on nephrolithiasis diagnosis, interventions for nephrolithiasis and other clinically relevant comorbidities (see supplementary table) registered before study entry (from the Swedish Patient Register) and data on treatment with tumour necrosis factor inhibitors before study entry in AS patients (the Swedish Biologics Register) were used to describe baseline characteristics and to identify predictors of nephrolithiasis intervention.

**Statistical analysis**

Crude incidence rates (IRs) of definitive surgery for nephrolithiasis per 1000 person-years with 95% confidence intervals (CIs) were calculated for AS patients and for matched GPC subjects, overall. Dichotomous outcomes were compared using the chi-squared test. Based on IRs, incidence rate ratios with 95% CIs were calculated.

To identify predictors of nephrolithiasis interventions, multivariate binary logistic regression analyses were performed in the group of AS patients and GPCs with a diagnosis of nephrolithiasis during the study period, calculating odds ratios (ORs) and 95% CIs. Variables tested were chosen based on forward selection (if \( p < 0.10 \)) of a priori clinical important factors including comorbidities and extra-articular manifestations, i.e. a history at the start of follow-up (yes/no) of the following: atherosclerotic heart disease, hypertension, renal insufficiency, calcium metabolic disorders (hyperparathyroidism, hyperoxaluria, psoriasis, inflammatory bowel disease, uveitis, arthritis urica, cystinuria, hyperuricaemia), inflammation of the pelvis or ureter (KAT00 or KBT00), kidney disorders (glomerular, tubular and anatomical). The frequency of obesity and diabetes was similar in the two groups.

Sensitivity analyses studying subsets of AS patients and corresponding controls were performed in subgroups of patients with no prior or recurrent nephrolithiasis diagnosis. A two-tailed \( p \) value less than 0.05 was considered significant.

**Results**

**Baseline characteristics**

In total, 8572 AS patients and 39,639 matched GPC subjects were included in the study and contributed 49,959 person-years [mean 5.8, interquartile range (IQR) 3.3–8.7 person-years] and 225,221 person-years (mean 5.7, IQR 3.1–8.6 person-years), respectively. The mean age of AS patients and GPC subjects at study entry was 46 years (IQR 36–56 years) and 65% were male. Since some AS patients in this unselected study population received their diagnosis years before study entry, the mean age is higher than what would be expected from an incident AS population. Baseline characteristics of AS patients and GPC subjects are presented in Table 1. Baseline data were complete except for data on level of education, which were missing in 1.2% (GPC \( n = 457, \) AS \( n = 101 \)). The baseline data on demographics and extra-articular comorbidities for the AS group resemble a population of moderate to severe AS. As would be expected, AS patients and GPCs differed at study entry regarding history of AS-related comorbidities. AS patients also had a higher frequency of prior nephrolithiasis diagnosis and prior interventions for nephrolithiasis and upper urinary tract disorders (glomerular, tubular and anatomical). The frequency of obesity and diabetes was similar in the two groups.

Table 1. Baseline characteristics of the ankylosing spondylitis (AS) cohort and matched general population comparator (GPC) subjects at study entry.

| Characteristic                        | AS cohort \( (n = 8572) \) | GPC subjects \( (n = 39,639) \) |
|--------------------------------------|-----------------------------|----------------------------------|
| Male, % \( (n) \)                    | 66.3 (5597)                 | 65.0 (25,769)                    |
| Age at study entry (years), mean (IQR) | 46.4 (36.0–56.0)           | 46.1 (36.0–56.0)                 |
| Education (years), % \( (n) \)       |                             |                                  |
| ≤ 9                                  | 21.7 (1859)                 | 21.3 (8436)                      |
| 10–12                                | 47.2 (4042)                 | 46.6 (18,474)                    |
| ≥ 12                                 | 30.0 (2570)                 | 31.0 (12,272)                    |
| Missing                              | 1.2 (101)                   | 1.2 (457)                        |
| Medication, % \( (n) \)              |                             |                                  |
| Anti-TNF                             | 8.5 (730)                   | N/A                              |
| Prior surgery for nephrolithiasis, % \( (n) \) | 0.4 (37) | 0.2 (68) |
| Comorbidities, % \( (n) \)           |                             |                                  |
| Uveitis                              | 11.4 (978)                  | 0.2 (93)                         |
| Renal insufficiency                  | 7.5 (644)                   | 3.6 (1428)                       |
| Hypertension                         | 7.3 (626)                   | 3.5 (1389)                       |
| Inflammatory bowel disease           | 6.0 (515)                   | 0.8 (303)                        |
| Ischaemic heart disease              | 5.1 (434)                   | 3.2 (1276)                       |
| Diabetes                             | 3.9 (337)                   | 3.2 (1267)                       |
| Psoriasis                            | 3.2 (271)                   | 0.5 (211)                        |
| Nephrolithiasis                      | 1.6 (134)                   | 0.7 (273)                        |
| Calcium metabolic disorders          | 1.2 (100)                   | 0.4 (154)                        |
| Glomerular, tubular and anatomical   | 1.0 (88)                    | 0.4 (31)                         |
| upper urinary tract disorders        |                             |                                  |
| Arthritis urica, cystinuria,         |                             |                                  |
| hyperoxaluria                        | 0.4 (163)                   | 0.1 (38)                         |
| Obesity                              | 0.4 (37)                    | 0.4 (173)                        |

Abbreviations: IQR = Interquartile range; TNF = Tumour necrosis factor; RR = Rate ratio; N/A = Not applicable.

Nephrolithiasis interventions in patients with ankylosing spondylitis versus general population comparators

Table 2 summarizes the number of first surgical procedures for nephrolithiasis, time at risk, and crude IRs in AS patients and GPCs during the study period. In total, 114 first interventions (maximum one per person during follow-up) were recorded in the overall GPC cohort during the study period, corresponding to a crude IR of 0.5 per 1000 person-years (95% CI 0.4–0.6). By contrast, 72 first interventions were recorded in the AS cohort, corresponding to a crude IR of 1.4 per 1000 person-years (95% CI 1.1–1.8). The rate ratio of
a first surgical intervention for nephrolithiasis in overall AS patients compared to GPCs was 2.9 (95% CI 2.1–3.8).

A diagnosis of nephrolithiasis was recorded in 466 of GPCs compared to 250 of the AS patients during the study period. All AS patients and GPCs who underwent a surgical intervention for nephrolithiasis also had a registered diagnosis of nephrolithiasis during the study period. But not all patients with a diagnosis of nephrolithiasis underwent surgery. Thus, 24% of overall GPCs with a diagnosis of nephrolithiasis during the study period underwent a surgical intervention, compared to 29% of overall AS patients (p = 0.21).

The distribution of the different surgical interventions for nephrolithiasis in GPCs and AS patients is illustrated in Figure 2, showing no significant difference in procedures performed in GPC and AS subjects (p = 0.80). ESWL was the dominating type of intervention in AS (63%) and in GPCs (64%), followed by ureteroscopic procedures (26% and 25%, respectively) and PCNL (9% and 6%, respectively). Open surgery constituted only 1% in AS patients and 2% in GPCs.

Note that all procedures performed during the study period are reported in Figure 2, including repeated procedures in the same individual, giving a higher number of total procedures than in Table 2.

### Predictors of nephrolithiasis intervention

To identify predictors of intervention for nephrolithiasis, multivariate analyses of baseline characteristics were performed in the subgroup experiencing nephrolithiasis during the study period. This revealed prior nephrolithiasis diagnosis (OR 3.3, 95% CI 1.97–5.62), increasing age (OR 1.02, 95% CI 1.01–1.03) and atherosclerotic cardiac disease (OR 2.0, 95% CI 1.03–3.91) as predictors of intervention in AS patients and GPC subjects. Gender and other baseline comorbidities showed no significant association with increased risk of intervention for nephrolithiasis in AS patients and GPC subjects.

### Sensitivity analyses

Sensitivity analyses were performed in subgroups of nephrolithiasis patients with and without recurrent nephrolithiasis, i.e. registered nephrolithiasis diagnosis both before and during the study period. The subgroup of AS patients with recurrent nephrolithiasis showed a significantly higher

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**Table 2.** Number of events and incidence rates of first surgical intervention for nephrolithiasis during the study period in patients with ankylosing spondylitis (AS) (n = 8572) compared to general population comparators (GPC) (n = 39,639), overall and stratified by status on prior nephrolithiasis at study entry.

|                     | No. of surgical procedures/py | Time at risk (years), median (IQR) | Crude IR per 1000 py (95% CI) | RR (95% CI) |
|---------------------|------------------------------|------------------------------------|-----------------------------|-------------|
| Overall             | GPC 114/225,221              | 6.2 (3.1–8.6)                      | 0.5 (0.4–0.6)               | 2.9 (2.1–3.8) |
|                     | AS 72/49,960                 | 6.4 (3.3–8.7)                      | 1.4 (1.1–1.8)               |             |
| Prior nephrolithiasis: no | GPC 100/224,143 | 6.2 (3.1–8.6)                      | 0.4 (0.3–0.5)               |             |
|                     | AS 47/49,438                 | 6.5 (3.4–8.7)                      | 1.0 (0.7–1.3)               |             |
| Prior nephrolithiasis: yes | GPC 14/1078      | 3.6 (1.6–5.8)                      | 12.0 (7.1–21.8)             |             |
|                     | AS 25/522                    | 3.5 (1.1–6.4)                      | 47.9 (31.0–70.7)            |             |

Person-years (py) defined as starting at the date of entry into study (time of AS diagnosis, earliest 1 January 2001) until first of death, emigration, nephrolithiasis diagnosis or end of study (31 December 2009).

Abbreviations: IQR = Interquartile range; IR = Incidence rate; CI = Confidence interval; RR = Rate ratio.

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**Figure 2.** Distribution of procedures for nephrolithiasis (n = 105) in patients with ankylosing spondylitis (AS) (n = 8572) compared to procedures (n = 148) in general population comparators (GPC) (n = 39,639) during the study period. Note that all procedures performed during the study period are reported in this figure, including repeated procedures in the same individual.

Abbreviations: ESWL = Extracorporeal shockwave lithotripsy; PCNL = Percutaneous nephrolithotomy; RIRS = Retrograde intrarenal surgery; URS = Ureteroscopic procedures.
fraction of 57% of patients undergoing an intervention in comparison to 38% in GPCs with recurrent nephrolithiasis ($p < 0.01$) and 22% in AS patients with no prior nephrolithiasis ($p < 0.01$). Consequently, in subjects with recurrent nephrolithiasis the rate ratio of intervention in AS patients compared to GPCs was 3.7 (95% CI 1.8–7.7), compared to 2.1 (95% CI 1.5–3.0) in AS patients with no prior nephrolithiasis, as seen in Table 2.

Within the group of GPC, the surgical fraction of 38% in GPCs with recurrent nephrolithiasis was significantly higher than the 23% of GPC subjects with no prior stone ($p < 0.01$).

### Discussion

To the authors’ knowledge, this is the first study to describe the frequency and distribution of surgical interventions in AS patients compared to matched GPC subjects based on nationwide prospective data.

This study demonstrates a nearly three-fold increased frequency of definitive surgery for nephrolithiasis in AS patients compared to the general population. The distribution of the different surgical procedures for nephrolithiasis was similar for AS patients and GPCs, with ESWL as the dominating intervention.

In subjects with nephrolithiasis, the proportion that underwent at least one nephrolithiasis-specific intervention during the study period (around 25%) did not differ between AS and their matched GPCs. Thus, the increased frequency of surgery in AS patients is to a large extent explained by the more than two-fold risk of nephrolithiasis, which was demonstrated in a previous study [12]. However, the fraction of AS patients with recurrent nephrolithiasis that underwent surgery was significantly higher than for GPCs with recurrent nephrolithiasis.

Increasing age, previous nephrolithiasis diagnosis and atherosclerotic cardiac disease were all associated with increased risk of intervention in AS patients and GPC subjects diagnosed with nephrolithiasis during the study period.

The finding that approximately one out of four patients with a nephrolithiasis diagnosis underwent an intervention during a mean follow-up of about 6 years is somewhat lower than the 38% that was recently reported by Seklehner et al. in a retrospective cohort of patients with nephrolithiasis during the same period [17]. This difference may partly be explained by the fact that only patients with ureteric stones were included in that study, but may also reflect differences in practice patterns between Sweden and North America.

In this study, ESWL was found to be the dominant modality of intervention, which is consistent with what has been reported in previous studies. However, more recent reports on temporal changes in practice patterns in North America indicate a shift in the choice of treatment, with increased use of ureteroscopy and a reciprocal decrease in the use of ESWL [7,9,10,17]. Based on the results of this study, this change does not seem to have emerged in the practice patterns of nephrolithiasis surgery in Sweden up until 2009. However, the clinical experience of the authors indicates that a similar shift from ESWL to ureteroscopic procedures has taken place during the past 5 years. Owing to the sample size and duration of this study, the data do not allow any conclusions to be drawn on temporal changes in the choice of modality during the period studied.

The coverage and precision of classification in the national Swedish registries are generally high [12,13,18–20]. As mentioned, the diagnosis of AS patients in the current report was found to have high validity, as described in a previous study [16]. The definition of definitive surgery for nephrolithiasis in this study resembles the definition used by other groups [9,10].

Furthermore, considerations on the coverage and validity of data sources, risk of misclassification, bias and potential confounding regarding the diagnosis of AS, nephrolithiasis and comorbidities are discussed in previous studies on this cohort [12,13,18].

### Interpretation and generalizability

The finding of a nearly three-fold increased risk of nephrolithiasis surgery in AS patients supports the validity of the previously reported increased risk of nephrolithiasis in AS patients [12].

Based on the present study, it appears that upper urinary tract stones are managed similarly in overall AS patients as in the general population. AS patients with recurrent nephrolithiasis underwent surgery 3.7 times as often as GPC subjects with recurrent nephrolithiasis, indicating that this subgroup of AS patients may have more complicated stone disease. However, the present study design does not allow any definite conclusions on this matter.

The fact that AS patients and GPCs with a diagnosis of nephrolithiasis in combination with atherosclerotic cardiac disease had a four-fold risk of intervention prompts speculation that treating physicians are more cautious in managing these patients, leading to a lower threshold for intervention.

Future studies on these questions, as well as studies on the causative mechanisms behind the increased risk of stone formation in AS patients, may not only help in the understanding of nephrolithiasis in AS patients, but also give clues to the understanding of AS and nephrolithiasis in general.

In conclusion, the frequency of definitive surgical interventions for nephrolithiasis in AS patients compared to the general population is increased nearly three-fold, which is partly explained by a more than two-fold increased risk of nephrolithiasis in AS patients. The fraction and choice of surgical management of nephrolithiasis are similar in overall AS patients and GPCs, but patients with recurrent nephrolithiasis undergo surgery more often than other subgroups.

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of the results and editing of the manuscript, and read and approved the final manuscript.

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**Declaration of interest:** AKJ affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and no significant discrepancies from the study protocol as planned were encountered. No potential conflict of interest was reported by the authors.

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**Supplementary material available online**

Supplementary table.