



**Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence - a cohort study**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004051
Article Type:	Research
Date Submitted by the Author:	18-Sep-2013
Complete List of Authors:	Guldberg, Rikke; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Kesmodel, Ulrik; Aarhus University Hospital, Department of Obstetrics and Gynecology Brostrøm, Søren; Danish Health and Medicines Authority, Department of Hospital Services and Emergency Management Kærlev, Linda; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Hansen, Jesper; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Hallas, Jesper; University of Southern Denmark, Research Unit of Clinical Pharmacology Nørgård, Bente; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology
<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology, Surgery
Keywords:	Urogynaecology < GYNAECOLOGY, SURGERY, Urinary incontinences < UROLOGY, Urinary tract infections < UROLOGY, Antibiotics, Clinical epidemiology

SCHOLARONE™  
Manuscripts

## Title page

# Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence – a cohort study

Rikke Guldberg<sup>1,2</sup>, Ulrik Schiøler Kesmodel<sup>3</sup>, Søren Brostrøm<sup>4</sup>, Linda Kærlev<sup>1,2</sup>, Jesper Kjær Hansen<sup>1,2</sup>, Jesper Hallas<sup>5</sup>, Bente Mertz Nørgård<sup>1,2</sup>

<sup>1</sup>Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

<sup>2</sup>Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

<sup>3</sup>Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark

<sup>4</sup> Department of Hospital Services and Emergency Management, Danish Health and Medicines Authority, Copenhagen, Denmark

<sup>5</sup> Research Unit of Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark

## Corresponding author

Rikke Guldberg, Center for Clinical Epidemiology, Odense University Hospital, Sdr. Boulevard 29, entrance 101, 4<sup>th</sup>, 5000 Odense C, Denmark.

Mail: [Rikke.Guldberg.Soerensen@rsyd.dk](mailto:Rikke.Guldberg.Soerensen@rsyd.dk)

Phone: +45 3070 3692

Fax: +45 6591 7264

**Keywords:** antibiotics, clinical epidemiology, surgery, urinary incontinence, urinary tract infection

**Word counts:** 3.044

## Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CRN = Civil Registration Number

ICD = International Classification of Diseases

MUS = mid-urethral sling

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

UTI = Urinary tract infection

## Abstract

**Objective** To describe the use of antibiotics for urinary tract infection (UTI) before and after surgery for urinary incontinence (UI); and for those with use of antibiotics before surgery, to estimate the risk of treatment for a postoperative UTI, relative to those without use of antibiotics before surgery.

**Design** A historical population-based cohort study

**Setting** Denmark

**Participants** Women (age $\geq$ 18 years) with a primary surgical procedure for UI from the county of Funen and the Region of Southern Denmark from 1996 throughout 2010. Data on redeemed prescriptions of antibiotics +/- 365 days from the date of surgery were extracted from a prescription database.

**Main outcome measures** Use of antibiotics for UTI in relation to UI surgery, and the risk of being a postoperative user of antibiotics for UTI among preoperative users.

**Results** A total of 2,151 women had a primary surgical procedure for UI; of these 496 (23.1%) were preoperative users of antibiotics for UTI. Among preoperative users, 129 (26.0%) and 215 (43.3%) also redeemed prescriptions of antibiotics for UTI within 0-60 and 61-365 days after surgery, respectively. Among preoperative non-users, 182 (11.0%) and 235 (14.2%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antibiotics for UTI was a strong risk factor for postoperative treatment for UTI, both within 0-60 days [OR, adjusted = 2.6 (95% confidence interval (CI) 2.0-3.5)] and within 61-365 days [OR, adjusted = 4.5 (95% CI 3.5-5.7)].

**Conclusions** One in four women undergoing surgery for UI was treated for UTI before surgery, and half of them had a continuing tendency to UTIs after surgery. Use of antibiotics for UTI before

1  
2  
3  
4 surgery was a strong risk factor for antibiotic use after surgery. In women not using antibiotics for  
5  
6 UTI before surgery only a minor proportion initiated use after surgery.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Introduction

Urinary tract infection (UTI) is a common problem in women, and 40% of women will have a UTI during life-time – and of these 27% will have recurrent UTI within 12 months (1). There are several risk factors for UTI and recurrent UTI; e.g. high age, urogenital atrophy, and urinary incontinence (UI) (2,3). UI is associated with UTI (2,4), and UTI might be regarded as a comorbid condition in women with UI due to a number of factors including poor perineal hygiene (5). Thus, it is not surprising that UTI is seen in women with UI, but no studies have so far examined the burden of UTI in women undergoing surgery for UI in a population based setting.

It is also well known that UTI is common after UI surgery. Risk factors of postoperative UTI include previous recurrent UTI, postoperative catheterization, positive urine cultures at day of surgery, and preoperative postvoid residual (6–9). UTI after UI surgery might occur among 34% of the women - depending on diagnostic methods and criteria (8,10–16), and surgery related infections occur within 2 months (17). Thus, while some knowledge of UTI exists in the short term perspective after UI surgery, there is only little evidence on the frequency of UTI in a more long term perspective after UI surgery (8).

The purpose of this study was to examine the use of antibiotics for UTI before and after surgery for UI, and among women using antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term perspective.

## Materials and Methods

### *Study population and settings*

Women were included in the study if they had a primary surgical procedure for UI within the period of 1 January 1996 through 31 December 2010. Data on performed procedures were retrieved from the Danish National Patient Registry (NPR) (18) according to codes listed in Appendix 1. The surgical procedures were performed in one of four hospitals in the county of Funen, Denmark, between 1 January 1996 and 31 December 2006, or for the period 2007 through 2010 in one of 13 hospitals in the new Region of Southern Denmark (including Funen). The extension of the area was due to a change in the organisation of the health care system in 2007, including a structural change from 14 counties to five regions. Women with concomitant or prior surgery for pelvic organ prolapse were included. Women younger than 18 years were excluded.

### *Data sources*

Data for this study were retrieved from three Danish registers: the NPR, Odense University Pharmacoepidemiologic Database (OPED), the Statistics Denmark. All Danish citizens are assigned a unique Civil Registration Number (CRN), which enables individual-level linkage across registries (19).

The NPR contains data on discharges from public hospitals in Denmark, and the completeness of recordings has been estimated to be 99.4% (20). Information available in the registry is the CRN, the dates of admission, date of discharge, and discharge diagnoses, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (21,22) as well as codes from the Danish classification system of surgical procedures (23).

Information on relevant drugs (antibiotics, and oestrogens) was retrieved from the OPED in the period 1995 to 2011 for the entire study population.

1  
2  
3  
4 The OPED is pharmacy-based and captures all reimbursed prescriptions, and contains person-  
5  
6 identifiable data with complete coverage on all computerized prescription reimbursements from the  
7  
8 County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended  
9  
10 to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution  
11  
12 of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and  
13  
14 the prescribing of drugs is very similar to the national average (24).

15  
16  
17 Prescription reimbursements are given independently of patient income to all legal inhabitants of  
18  
19 Denmark as a part of the National Health Service. Each record includes the CRN, the date of  
20  
21 purchase, a full account of what have been dispensed, including the brand name, and the  
22  
23 Anatomical Therapeutic Chemical (ATC) classification code. Information not included in the  
24  
25 prescription database is drugs sold over the counter or drugs not reimbursed by the county authority  
26  
27 (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level  
28  
29 and annual income were retrieved from the Danish Integrated Database for Labor Market Research  
30  
31 at Statistics Denmark, a database with annually updated socioeconomic data for each Danish  
32  
33 citizen, mainly supplied by tax authorities, educational institutions, and employment services (25).  
34  
35  
36  
37  
38  
39

#### 40 *Antibiotics under study*

41  
42 Included drugs were antibiotics traditionally used in Denmark exclusively or predominantly for the  
43  
44 treatment of UTI (Sulfamethizole [ATC J01EB02], Pivmecillinam [ATC J01CA08], Nitrofurantoin  
45  
46 [ATC J01XE01], Trimethoprim [ATC J01EA01], as well as Mecillinam [ATC J01CA11]) (26,27).  
47  
48 The indications for the prescribed drugs are not registered in the OPED; therefore pivampicillin and  
49  
50 amoxicillin were not included – as these antibiotics are also commonly used in treatment of upper  
51  
52 respiratory tract infections as well. Likewise, broader spectrum antibiotics such as cephalosporins  
53  
54 and quinolones were not included, as they are not commonly used for UTIs in Denmark.  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### *Exposed and unexposed cohorts*

Exposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions on antibiotics within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

### *Outcome data*

For both exposed and unexposed women, the outcome was use of antibiotics for UTI, defined as having redeemed at least one prescription for these antibiotics within 1) 60 days after the index date (short term postoperative users), and 2) 61 days to 365 days after the index date (long term postoperative users). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

### *Covariates*

The use of antibiotics might be affected by age, type of surgery, use of oestrogen, comorbidity, calendar time, and the individuals' ability to pay for the medicine might be affected by educational level, and annual income. Therefore, these variables were included in the analysis as potential confounders.

*Type of procedures:* The types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-

1  
2  
3  
4 urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types  
5  
6 of UI surgeries.

7  
8 *Oestrogen*: Use of oestrogens [ATC G03C] was included in the analyses as a confounder.

9  
10 To adjust for preoperative oestrogen use, preoperative users of oestrogens were defined as women  
11  
12 who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and  
13  
14 non-users were defined as those who had no preoperative oestrogen use during the same period.

15  
16 Both local and systemic oestrogens were included.

17  
18 *Comorbidity*: The comorbidity was classified according to the validated, well-known and widely  
19  
20 used Charlson comorbidity index (CCI) (29–31), which assigns different weights (1, 2, 3, and 6) to  
21  
22 20 different disease categories specified by medical condition and severity (for example, diabetes,  
23  
24 cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). The CCI  
25  
26 was computed based on each woman's complete hospital discharge history from the NPR since  
27  
28 1977. A categorised version of the CCI score values was used: 0 (low), 1-2 (medium) and 3+ (high)  
29  
30 (32).  
31  
32  
33  
34

35  
36 *Education and income*: Information on educational level and annual income for each woman was  
37  
38 retrieved as a measure of socioeconomic status. Educational level was categorised according to the  
39  
40 highest attained educational level in the year of surgery: "Basic" (basic school/high school  
41  
42 education: 7-12 years of primary, secondary and grammar-school education), "Secondary"  
43  
44 (vocational education, 10-12 years of education), and "Higher" (a university degree or an  
45  
46 examination in another higher institution requiring an average total of 13 years or more) (28).

47  
48 On the basis of quartiles of annual income for each woman in the year of her surgery, we  
49  
50 categorised women in low (1<sup>st</sup> quartile), medium (2<sup>nd</sup> and 3<sup>rd</sup> quartile), and high income (4<sup>th</sup>  
51  
52 quartile).  
53  
54  
55  
56  
57  
58  
59  
60

### *Statistical analysis*

The use of antibiotics for UTI within the first 365 days after surgery for exposed and unexposed cohorts was illustrated in a flowchart. We also constructed contingency tables for the main study variables, and computed odds ratios (ORs), with 95% confidence intervals (CI).

To analyse the significance of preoperative antibiotic use as risk factor of postoperative use (within 60 days and within 61-365 days after surgery), adjusted ORs were estimated by means of multivariate logistic regression models.

Adjustment was made for age (18-39, 40-59, and  $\geq 60$  years (reference)), type of procedures (toMUS (reference), rpMUS, bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365 days preceding surgery (No (reference), yes).

Stratified analyses were performed according to use of oestrogens before surgery to examine the association between the use of antibiotics for UTI in oestrogen users vs. oestrogen non-users.

All analyses were performed using Stata Release 12.0.

## Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010; 2,073 had a solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse.

Of the 2,151 women, a total of 1,655 (76.9%) women did not use antibiotics for UTI within in 365 days prior to surgery, while 496 (23.1%) did, and the majority (376/496=75.8%) redeemed  $\leq 2$  prescriptions preoperatively. The use of symptom-relieving drugs within 365 days after surgery is detailed for the exposed and unexposed cohorts in Figure 1.

### *Women having redeemed prescriptions for antibiotics for UTI before surgery (exposed)*

Of the 496 women with prior use of antibiotics for UTI, 129 (26.0%) redeemed a prescription for antibiotics for UTI within 0-60 days after surgery, and of these, 85 (65.9%) also within 61-365 days after surgery (Figure 1). A total of 215 (43.3%) continued to redeem prescriptions for antibiotics within 61-365 days (Figure 1).

### *Women with no usage of symptom-relieving drugs before surgery (unexposed)*

Out of the 1,655 women who did not redeem prescription before surgery, 182 (11.0%) women had a short term use of antibiotics for UTI after surgery; and of these, 64 women were also long term users (Figure 1). Among unexposed without short term postoperative use of antibiotics, 171 (10.3%) became long term postoperative user (Figure 1). The total of women with long term antibiotic use was 235 (14.2%).

### *Comparison of exposed and unexposed cohorts*

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedure was toMUS accounting for approximately half of the procedures performed in both the exposed and the unexposed group. The most commonly prescribed drugs prior to surgery were sulfamethizol and pivmecillinam. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, and to have higher comorbidity indices. There was no difference in educational level or personal annual income.

The unadjusted OR of a prior antibiotic user being a postoperative user short and long term was 2.8 (95% CI 2.2-3.7), and 4.6 (95% CI 3.7-5.8), respectively. The adjusted OR of being short and long term user of symptom-relieving drugs after surgery was 2.6 (95% CI 2.0-3.5), and 4.5 (95% CI 3.5-5.7), respectively (Table 2). Thus, adjustment for confounders did virtually not change the relative risk estimates. The details from logistic regression models are presented in Table 2 showing the impact of each prognostic factor included. Regarding short term use the strongest risk factors were procedure types (rpMUS/others), high comorbidity index, and preoperative antibiotic use.

Preoperative use of antibiotics for UTI was the strongest risk factor of long term postoperative use.

Stratified analyses according to the use of oestrogens before surgery showed that among users of oestrogen, the adjusted OR for short and long term use of antibiotics for UTI after surgery increased to 3.3 (95% CI 2.3-4.8) and 5.2 (95% CI 3.7-7.3), respectively, Table 3.

## Discussion

Among 2,151 women undergoing surgery for UI nearly one fourth had redeemed at least one prescription of antibiotics for UTI preoperatively, and among preoperative users nearly half of the women also redeemed prescriptions of antibiotics for UTI within 61-365 days after surgery. Among preoperative users of antibiotics we found a 2-3 fold increased risk of short term use of antibiotics for UTI after surgery, and a 4-5 fold increased risk of being long term user. In women not using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics after surgery. To ensure that our results were not influenced by effect modification of oestrogen use we stratified our analyses for preoperative use of oestrogen. In both strata we found an increased risk of postoperative antibiotic use for the exposed women. The risk estimates for short- and long term use were, however, higher among women using oestrogen preoperatively compared to women without prior oestrogen use.

The proportion of women with concomitant surgery for pelvic organ prolapse in our cohort of women with UI surgery was low, and this was as expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (34). Thus, our results were not influenced by a mixed cohort with both UI surgery and pelvic organ prolapse surgery.

Our study has several strengths: 1) it is population-based in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) the source of procedure codes in the NPR has high coverage and validity - The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a high quality of the data with positive predictive values of 94-100% (35-37), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (24), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in

1  
2  
3  
4 the follow up period for all included women, 6) outcome data on postoperative antibiotic  
5 prescriptions are recorded independently of prior antibiotic use, thus preventing differential  
6 misclassification of the outcome, 7) the antibiotics included in this study are UTI specific and are  
7 drugs of choice in Denmark for treating UTI, and finally 8) the surgical procedures included have  
8 no other indications than UI, which strongly limits the number of alternative interpretations of our  
9 findings. Furthermore, the exclusion of antibiotics with other indications than UTI may even have  
10 led to an underestimation of the risk of UTI.

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

There are possible limitations to our study. We have no information on perioperative use of antibiotic, antibiotic given while the patient was still hospitalised, or results of urine culture. To prevent UTI and other postoperative infections a perioperative single-dose of intravenous antibiotic is often used in Denmark (38). However, perioperative antibiotic use is unlikely to be much different between exposed and unexposed cohorts and will thus not bias our relative risk estimates. In the short term perspective after surgery we had no knowledge of postoperative catheter usage which is a limitation, especially since postoperative UTI is associated with catheter usage in the postoperative period (39,40), but again we have no reasons to believe that use of catheters differed among exposed and unexposed cohorts. We were not able to control for all potential confounders such as body mass index, parity, intraoperative bladder perforation, or precise menopausal status, but the importance of these factors for the association examined in this study is not clear. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, or on urodynamic study, and it could have been interesting to further examine the users of UTI antibiotics (both before and after surgery) according to the type of UI symptomatology.

It is surprising that among women having UVIs before UI surgery, half of them have a continuing tendency to UTIs after surgery. This is not explained by recurrent UI surgery in the study period of

1  
2  
3  
4 one year after surgery as only approximately 5% of the women experienced a new surgery in our  
5  
6 population. Possible explanations for the continuing tendency to UTI could be a genetic  
7  
8 predisposition for UTI, an anatomic predisposition for UTI, or an increased awareness of UTI for  
9  
10 both the women and their doctor.

11  
12 Based on the flowchart in our study, we found a tendency to continuing UTI among women with  
13  
14 preoperative antibiotic use in both short- and long term postoperatively. To our knowledge, this is  
15  
16 the largest, and only population-based, study examining the use of antibiotics for UTI in relation to  
17  
18 surgery for UI and addressing the risk of both short- and long term postoperative use of antibiotics  
19  
20 for UTI among women with preoperative UTI. In addition, our study provides knowledge about  
21  
22 which other factors than preoperative antibiotic were important for postoperative antibiotic use for  
23  
24 UTI. We found that for short term use procedure type (rpMUS, others), and high comorbidity were  
25  
26 risk factors, and for long term use high comorbidity was a risk factor. Our study also showed that  
27  
28 educational level and personal income did not seem to influence the risk of postoperative antibiotic  
29  
30 use.  
31  
32  
33  
34

35 Our study calls for further studies within this area – studies examining UTI before and after surgery  
36  
37 according to different types of UI (stress UI, urgency UI, mixed UI), UTI in relation to surgery in  
38  
39 especially post-menopausal women, issues regarding recurrent UTI and UI surgery, and if  
40  
41 prophylactic antibiotic use (perioperative intravenous/prolonged oral antibiotics) could reduce the  
42  
43 risk of postoperative UTI after UI surgery in a short- and long term perspective.  
44  
45

46 In conclusion, we found that one in four women undergoing surgery for UI was treated for UTI  
47  
48 before surgery, and half of these women continued the tendency of UTI after surgery. In women not  
49  
50 using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI  
51  
52 after surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of  
53  
54 these antibiotics before surgery.  
55  
56  
57  
58  
59  
60



1  
2  
3  
4 **Acknowledgement** None  
5

6  
7 **Funding** This study was funded by 1) Nordic Urogynaecology Association (NUGA) Research  
8  
9 Grant 2) A. P. Møller and Chastine Mc-Kinney Møller Foundation for General Purposes 3) Center  
10  
11 for Clinical Epidemiology, Odense University Hospital, and 4) Region of Southern Denmark  
12  
13

14  
15 **Financial disclaimer/Conflicts of interest** None  
16

17  
18  
19 **Contributors** All authors have drafted the article, revised it critically for important intellectual  
20  
21 content, and approved the final version to be published. All authors are responsible for the study  
22  
23 concept and design, and participated in the interpretation of data. RG is the guarantor and has full  
24  
25 access to all of the data in the study.  
26  
27

28  
29 **Competing interests** "All authors have completed the ICMJE uniform disclosure form at  
30  
31 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
32  
33 work; no financial relationships with any organisations that might have an interest in the submitted  
34  
35 work in the previous three years.  
36  
37

38  
39  
40 **Ethical approval** The study was approved by the Danish Data Protection Agency (no. 2009-41-  
41  
42 3564). According to Danish law, ethical review board approval or patient consent are not required  
43  
44 for register-based studies.  
45  
46

47  
48  
49 **Copyright** The Corresponding Author has the right to grant on behalf of all authors and does  
50  
51 grant on behalf of all authors, [a worldwide licence](#) to the Publishers and its licensees in perpetuity,  
52  
53 in all forms, formats and media (whether known now or created in the future), to i) publish,  
54  
55 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other  
56  
57  
58  
59  
60

1  
2  
3  
4 languages, create adaptations, reprints, include within collections and create summaries, extracts  
5  
6 and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the  
7  
8 Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic  
9  
10 links from the Contribution to third party material where-ever it may be located; and, vi) licence  
11  
12 any third party to do any or all of the above.  
13

14  
15  
16  
17 **Data sharing** According to the Danish Data Protection Agency, we are not allowed to share our  
18  
19 data from the Danish National Patient Registry. This would require a special approval from both the  
20  
21 Danish Data Protection Agency and the Statens Serum Institut who provides the data from the  
22  
23 Danish National Patient Registry.  
24  
25  
26  
27

### 28 29 **Article Summary:**

30  
31 **Article focus:** Urinary incontinence is a prevalent disorder among women, and surgery is one of  
32  
33 the major options for treatment. This study focus on the use of antibiotics for urinary tract infection  
34  
35 both before and after surgical treatment of urinary incontinence, and among women using  
36  
37 antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term  
38  
39 perspective.  
40  
41  
42

### 43 **Key messages:**

44  
45 One in four woman undergoing surgery for UI was treated for urinary tract infection (UTI) before  
46  
47 surgery, and half of these women continued the tendency of UTIs after surgery. In women not using  
48  
49 antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI after  
50  
51 surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of these  
52  
53 antibiotics before surgery.  
54  
55  
56  
57  
58  
59  
60

**Strengths and limitations of this study:**

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on symptomatology, catheter usage, preoperative antibiotics or urine culture.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figure 1** Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery. Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.

For peer review only

**Table 1** Baseline characteristics of all included women (N=2,151) having a primary surgical procedure for UI in Denmark, 1996-2010.

	Exposed <sup>a</sup> n=496	Unexposed <sup>b</sup> n=1,655
Mean age (±SD), years (At time of first UI surgery)	60.2 (±13.2)	54.2 (±12.4)
Age groups n (%)		
18-39	30 (6.1)	182 (11.0)
40-59	196 (39.5)	911 (55.1)
60-	270 (54.4)	562 (33.9)
Procedures n (%)		
rpMUS	140 (28.2)	535 (32.3)
toMUS	222 (44.8)	750 (45.3)
Bulking	110 (22.2)	250 (15.1)
Others	24 (4.8)	120 (7.3)
Concomitant prolapse surgery n (%)	12 (2.4)	66 (4.0)
Antibiotics before surgery n (%) <sup>*</sup>		
Sulfamethizol - J01EB02	299 (60.3)	-
Pivmecillinam - J01CA08	288 (58.1)	-
Nitrofurantoin - J01XE01	65 (13.1)	-
Trimethoprim - J01EA01	45 (9.1)	-
Mecillinam - J01CA11	0 (0)	-
Oestrogen users n (%) <sup>**</sup>		
No	211 (42.5)	997 (60.2)
Yes	285 (57.5)	658 (39.8)
Comorbidity (CCI) n (%)		
0	298 (60.1)	1,214 (73.4)
1-2	139 (28.0)	381 (23.0)
3+	59 (11.9)	60 (3.6)
Educational level n (%) <sup>***</sup>		
Basic	229 (47.4)	688 (42.3)
Secondary	170 (35.2)	600 (36.8)
Higher	84 (17.4)	340 (20.9)
Annual income n (%)		
Low (1 <sup>st</sup> quartile)	152 (25.0)	385 (23.3)
Middle (2 <sup>nd</sup> -3 <sup>rd</sup> quartile)	1,077 (50.0)	825 (49.9)
High (4 <sup>th</sup> quartile)	537 (25.0)	445 (26.9)
Year of surgery n (%)		
1996-2006	106 (21.4)	353 (21.3)
2007-2008	791 (37.5)	605 (36.6)
2009-2010	901 (41.1)	697 (42.1)

<sup>a</sup>Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery.

<sup>b</sup>Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.

<sup>\*</sup>Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.

<sup>\*\*</sup>Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

<sup>\*\*\*</sup>Unknown highest attained educational level: 40 women

Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 2** Risk factors of postoperative use of antibiotics. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii), long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,473	182	Reference	1,420	235	reference
Yes	367	129	2.6 (2.0-3.5)	281	215	4.5 (3.5-5.7)
Age group						
18-39	185	27	0.9 (0.5-1.5)	163	49	1.5 (0.9-2.3)
40-59	981	126	0.6 (0.5-0.9)	931	176	0.7 (0.5-0.9)
60+	674	158	Reference	607	225	reference
Procedure						
rpMUS	568	107	1.7 (1.1-2.7)	529	146	1.3 (0.9-1.9)
toMUS	849	123	Reference	782	190	reference
Bulking	315	45	1.4 (0.9-2.0)	278	82	1.1 (0.8-1.5)
Others	108	36	3.1 (1.6-5.9)	112	32	1.5 (0.8-2.8)
Preoperative use of oestrogen*						
No	1,059	149	Reference	992	216	reference
Yes	781	162	1.2 (0.9-1.6)	709	234	1.2 (0.9-1.5)
Comorbidity (CCI)						
0	1,328	184	Reference	1,241	271	reference
1-2	425	95	1.5 (1.1-2.0)	384	136	1.4 (1.1-1.8)
3+	87	32	3.1 (1.6-5.9)	76	43	1.5 (1.0-2.4)
Educational level**						
Basic	775	142	Reference	702	215	reference
Secondary	665	105	1.1 (0.8-1.5)	623	147	1.0 (0.7-1.1)
Higher	362	62	1.3 (0.9-2.0)	342	82	0.9 (0.6-1.3)
Annual income						
Low	434	103	Reference	404	133	reference
Middle	930	147	0.9 (0.6-1.2)	847	230	1.0 (0.8-1.3)
High	476	61	0.9 (0.6-1.4)	450	87	0.9 (0.6-1.3)
Year of surgery						
1996-2006	363	96	1.4 (0.9-2.2)	352	107	0.9 (0.7-1.1)
2007-2008	692	99	Reference	628	163	reference
2009-2010	785	116	1.0 (0.8-1.4)	721	180	1.0 (0.8-1.4)

\*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

\*\*Unknown highest attained educational level: 40 women

Abbreviations: Post op=postoperative, OR = odds ratio, CI = confidence interval , rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 3** Stratified analyses according to use of oestrogen before surgery for UI to examine the association between preoperative use of antibiotics for urinary tract infection and postoperative use.

Preop.	Preop.	Crude OR (95% CI)	Adj. OR* (95% CI)	Crude OR (95% CI)	Adj. OR* (95% CI)
oestrogen n	antibiotics n	Short term	Short term	Long term	Long term
Yes 943	Yes 285	3.5 (2.5-5.0)	3.3 (2.3-4.8)	5.2 (3.8-7.2)	5.2 (3.7-7.3)
	No 658				
No 1.208	Yes 211	2.0 (1.3-2.9)	2.0 (1.3-3.0)	3.8 (2.7-5.2)	3.7 (2.6-5.3)
	No 997				

\*Adjusted for age, procedure type, comorbidity, educational level, annual income, and calendar year of surgery.  
Abbreviations: Preop. = preoperative, Adj. = adjusted, OR = odds ratio, CI = confidence interval

## References

1. Foxman B. Recurring urinary tract infection: incidence and risk factors. *Am J Public Health* 1990;80:331–3.
2. Athanasiou S, Anstaklis A, Betsi GI, et al. Clinical and urodynamic parameters associated with history of urinary tract infections in women. *Acta Obstet Gynecol Scand* 2007;86:1130–5.
3. Hu KK, Boyko EJ, Scholes D, et al. Risk factors for urinary tract infections in postmenopausal women. *Archives of internal medicine* 2004;164:989–93.
4. Raz R, Gennesin Y, Wasser J, et al. Recurrent urinary tract infections in postmenopausal women. *Clin Infec Diseases* 2000;30:152–6.
5. Bodhare TN, Valsangkar S, Bele SD. An epidemiological study of urinary incontinence and its impact on quality of life among women aged 35 years and above in a rural area. *Indian IJU* 2010;26:353–8.
6. Fok CS, McKinley K, Mueller ER, et al. Day of surgery urine cultures identify urogynecologic patients at increased risk for postoperative urinary tract infection. *J Urol* 2013;189:1721–4.
7. Sutkin G, Alperin M, Meyn L, et al. Symptomatic urinary tract infections after surgery for prolapse and/or incontinence. *Int Urogynecol J* 2010;21:955–61.
8. Nygaard I, Brubaker L, Chai TC, et al. Risk factors for urinary tract infection following incontinence surgery. *Int Urogynecol J* 2011;22:1255–65.
9. Ingber MS, Vasavada SP, Firoozi F, Goldman HB. Incidence of perioperative urinary tract infection after single-dose antibiotic therapy for midurethral slings. *Urol* 2010;76:830–4.
10. Jackson D, Higgins E, Bracken J, Al E. Antibiotic Prophylaxis for Urinary Tract Infection After Midurethral Sling: A Randomized Controlled Trial. *Fem Pelv Med & Reconstr Surg* 2013;19:137–41.
11. Anger J, Litwin M, Wang Q, Al E. Complications of sling surgery among female Medicare beneficiaries. *Obstet Gynecol* 2007;109:707–14.
12. Stanford EJ, Paraiso MFR. A comprehensive review of suburethral sling procedure complications. *J Minimally Inv Gynecology* 1999;15:132–45.
13. LaSala C a, Schimpf MO, Udoh E, et al. Outcome of tension-free vaginal tape procedure when complicated by intraoperative cystotomy. *Am J Obstet Gynecol* 2006;195:1857–61.
14. Pugsley H, Barbrook C, Mayne CJ, Tincello DG. Morbidity of incontinence surgery in women over 70 years old: a retrospective cohort study. *BJOG* 2005;112:786–90.



15. Ward K, Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002;325:67.
16. Tamussino K, Hanzal E, Kolle D, Al E. Tension-free vaginal tape operation: results of the Austrian registry. *Obstet Gynecol* 2001;98:732–6.
17. Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association ( IUGA )/ International Continence Society ( ICS ) Joint Terminology and Classification of the Complications Related Directly to the Insertion of Prostheses ( Meshes , Implants , Tapes ) and Grafts in Female P. *Int Urogynecol J* 2011;22:3-15.
18. Lyng E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–5.
20. Andersen T, Madsen M, Jørgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:262–8.
21. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-8). Geneva, Switzerland; 1967.
22. World Health Organization. International Classification of Diseases - 10th revision (ICD-10) [Internet]. 2013. Available from: <http://www.who.int/classifications/ics/en/>
23. Nordic Medico-Statistical Committee. Classification of Surgical Procedures, version 1.15. 2010 no. 93.
24. Gaist D, Sørensen H, Hallas J. The Danish Prescription Registers. *Dan Med Bull*. 1997;44:445–8.
25. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011;39:95–8.
26. Bjerrum L, Grindsted P. How to treat uncomplicated cystitis? *Ugeskr Laeger*. 2000;162:197–8 [Danish].
27. Bjerrum L, Dessau R, Hallas J. Treatment failures after antibiotic therapy of uncomplicated urinary tract infections. A prescription study. *Scand J Primary Health Care*. 2002;20:97–101.
28. Dalton SO, Steding-Jessen M, Engholm G, et al. Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. *EurJ Cancer* 2008;44:1989–95.
29. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–83.

- 1  
2  
3  
4 30. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies  
5 using administrative databases. *Int J Epidemiol* 2000;29:891–8.  
6  
7 31. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10  
8 diagnostic coding used to assess Charlson comorbidity index conditions in the population-  
9 based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.  
10  
11 32. Thomsen R, Riis A, Christensen S, et al. Diabetes and 30-Day Mortality From A Danish  
12 population-based cohort study. *Diabetes Care*. 2006;29:805–10.  
13  
14 33. Svenningsen R, Borstad E, Spydslaug AE, et al. Occult incontinence as predictor for  
15 postoperative stress urinary incontinence following pelvic organ prolapse surgery. *Int*  
16 *Urogynecol J* 2012;23:843–9.  
17  
18 34. Andersen T, Madsen M, Loft A. Validity of surgical information from the Danish National  
19 Patient Registry with special attention to the analysis of regional variations in hysterectomy  
20 rates. *Ugeskr Laeger* 1987;149:2420–2 [Danish].  
21  
22 35. Mosbech J, Jørgensen J, Madsen M, et al. The national patient registry. Evaluation of data  
23 quality. *Ugeskr Laeger* 1995;157:3741–5 [Danish].  
24  
25 36. Ottesen M. Validity of the registration and reporting of vaginal prolapse surgery. *Ugeskr*  
26 *Laeger* 2009;171:404–8 [Danish].  
27  
28 37. Guldberg R, Brostrøm S, Hansen JK, et al. The Danish Urogynaecological Database:  
29 establishment, completeness and validity. *Int Urogynecol J* 2013;24:983–90.  
30  
31 38. Wald H, Ma A, Bratzler D, Al E. Indwelling Urinary Catheter Use in the Postoperative  
32 Period. *Arch Sur*. 2008;143:551–7.  
33  
34 39. Platt R, Polk B, Murdock B, Al. E. Risk factors for nosocomial urinary tract infection. *Am J*  
35 *of Epidemiol*. 1986;124:977–85.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

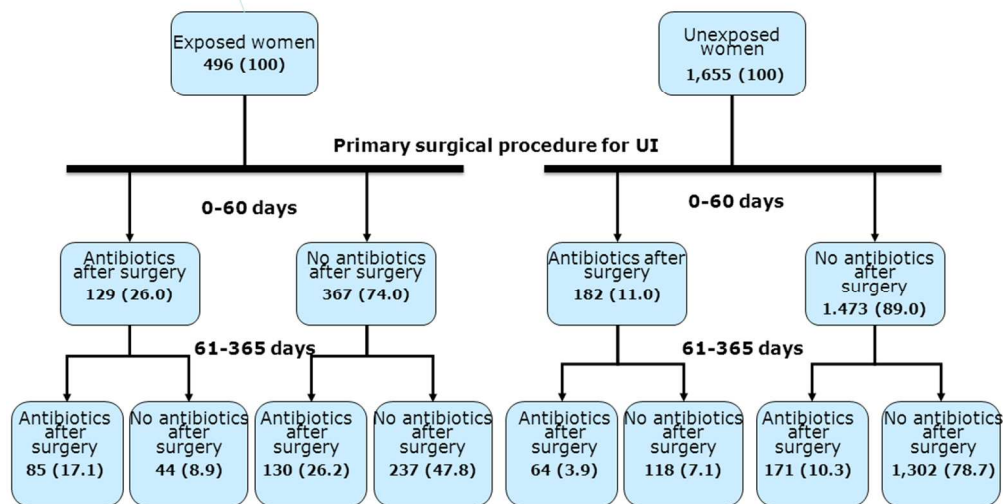
STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 – Title page
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	3+6-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+6-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10+11
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11 + Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 + Table 2
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	13
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI.

view only



**Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence - a cohort study**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004051.R1
Article Type:	Research
Date Submitted by the Author:	03-Jan-2014
Complete List of Authors:	Guldberg, Rikke; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Kesmodel, Ulrik; Aarhus University Hospital, Department of Obstetrics and Gynecology Brostrøm, Søren; Danish Health and Medicines Authority, Department of Hospital Services and Emergency Management Kærlev, Linda; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Hansen, Jesper; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology; Odense University Hospital, Center for Clinical Epidemiology Hallas, Jesper; University of Southern Denmark, Research Unit of Clinical Pharmacology Nørgård, Bente; Odense University Hospital, Center for Clinical Epidemiology; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology
<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology, Surgery
Keywords:	Urogynaecology < GYNAECOLOGY, SURGERY, Urinary incontinences < UROLOGY, Urinary tract infections < UROLOGY, Antibiotics, Clinical epidemiology

SCHOLARONE™  
Manuscripts

## Title page

# Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence – a cohort study

Rikke Guldborg<sup>1,2</sup>, Ulrik Schiøler Kesmodel<sup>3</sup>, Søren Brostrøm<sup>4</sup>, Linda Kærlev<sup>1,2</sup>, Jesper Kjær Hansen<sup>1,2</sup>, Jesper Hallas<sup>5</sup>, Bente Mertz Nørgård<sup>1,2</sup>

<sup>1</sup>Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

<sup>2</sup>Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

<sup>3</sup>Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark

<sup>4</sup>Department of Hospital Services and Emergency Management, Danish Health and Medicines Authority, Copenhagen, Denmark

<sup>5</sup>Research Unit of Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark

## Corresponding author

Rikke Guldborg, Center for Clinical Epidemiology, Odense University Hospital, Sdr. Boulevard 29, entrance 101, 4<sup>th</sup>, 5000 Odense C, Denmark.

Mail: [Rikke.Guldborg.Soerensen@rsyd.dk](mailto:Rikke.Guldborg.Soerensen@rsyd.dk)

Phone: +45 3070 3692

Fax: +45 6591 7264

**Keywords:** antibiotics, clinical epidemiology, surgery, urinary incontinence, urinary tract infection

**Word counts:** 3.044

## Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CRN = Civil Registration Number

ICD = International Classification of Diseases

MUS = mid-urethral sling

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

UTI = Urinary tract infection



## Abstract

**Objective** To describe the use of antibiotics for urinary tract infection (UTI) before and after surgery for urinary incontinence (UI); and for those with use of antibiotics before surgery, to estimate the risk of treatment for a postoperative UTI, relative to those without use of antibiotics before surgery.

**Design** A historical population-based cohort study

**Setting** Denmark

**Participants** Women (age $\geq$ 18 years) with a primary surgical procedure for UI from the county of Funen and the Region of Southern Denmark from 1996 throughout 2010. Data on redeemed prescriptions of antibiotics +/- 365 days from the date of surgery were extracted from a prescription database.

**Main outcome measures** Use of antibiotics for UTI in relation to UI surgery, and the risk of being a postoperative user of antibiotics for UTI among preoperative users.

**Results** A total of 2,151 women had a primary surgical procedure for UI; of these 496 (23.1%) were preoperative users of antibiotics for UTI. Among preoperative users, 129 (26.0%) and 215 (43.3%) also redeemed prescriptions of antibiotics for UTI within 0-60 and 61-365 days after surgery, respectively. Among preoperative non-users, 182 (11.0%) and 235 (14.2%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antibiotics for UTI was a strong risk factor for postoperative treatment for UTI, both within 0-60 days [OR, adjusted = 2.6 (95% confidence interval (CI) 2.0-3.5)] and within 61-365 days [OR, adjusted = 4.5 (95% CI 3.5-5.7)].

**Conclusions** One in four women undergoing surgery for UI was treated for UTI before surgery, and half of them had a continuing tendency to UTIs after surgery. Use of antibiotics for UTI before

1  
2  
3  
4 surgery was a strong risk factor for antibiotic use after surgery. In women not using antibiotics for  
5  
6 UTI before surgery only a minor proportion initiated use after surgery.  
7

### 8 9 **Article Summary:**

10  
11 **Article focus:** Urinary incontinence is a prevalent disorder among women, and surgery is one of  
12  
13 the major options for treatment. This study focus on the use of antibiotics for urinary tract infection  
14  
15 both before and after surgical treatment of urinary incontinence, and among women using  
16  
17 antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term  
18  
19 perspective.  
20  
21

### 22 23 **Key messages:**

24  
25 One in four woman undergoing surgery for UI was treated for urinary tract infection (UTI) before  
26  
27 surgery, and half of these women continued the tendency of UTIs after surgery. In women not using  
28  
29 antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI after  
30  
31 surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of these  
32  
33 antibiotics before surgery.  
34  
35

### 36 37 **Strengths and limitations of this study:**

38  
39 A population-based study.

40  
41 2,151 included women.

42  
43 High quality of data sources and complete information in the follow-up period for all included  
44  
45 women.  
46

47  
48 Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity,  
49  
50 educational level, and personal annual income.

51  
52 Redeemed prescriptions were used as a proxy for drug use.

53  
54 No data on symptomatology, catheter usage, preoperative antibiotics or urine culture.  
55  
56  
57  
58  
59  
60

## Introduction

Urinary tract infection (UTI) is a common problem in women, and 40% of women will have a UTI during life-time – and of these 27% will have recurrent UTI within 12 months (1). There are several risk factors for UTI and recurrent UTI; e.g. high age, urogenital atrophy, and urinary incontinence (UI) (2,3). UI is associated with UTI (2,4), and UTI might be regarded as a comorbid condition in women with UI due to a number of factors including poor perineal hygiene (5). Thus, it is not surprising that UTI is seen in women with UI, but no studies have so far examined the burden of UTI in women undergoing surgery for UI in a population based setting.

It is also well known that UTI is common after UI surgery. Risk factors of postoperative UTI include previous recurrent UTI, postoperative catheterization, positive urine cultures at day of surgery, and preoperative postvoid residual (6–9). UTI after UI surgery might occur among 6-38% of the women - depending on diagnostic methods and criteria (8,10–16), and surgery related infections occur within 2 months (17). Thus, while some knowledge of UTI exists in the short term perspective after UI surgery, there is only little evidence on the frequency of UTI in a more long term perspective after UI surgery (8).

The purpose of this study was to examine the use of antibiotics for UTI before and after surgery for UI, and among women using antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term perspective. This topic is highly clinical relevant in the counselling of women prior to surgery for UI: What can they expect of postoperative complications? Can preoperative drug users expect to continue drug use after surgery?

## Materials and Methods

### *Study population and settings*

Women were included in the study if they had a primary surgical procedure for UI within the period of 1 January 1996 through 31 December 2010. Data on performed procedures were retrieved from the Danish National Patient Registry (NPR) (18) according to codes listed in Appendix 1. The surgical procedures were performed in one of four hospitals in the county of Funen, Denmark, between 1 January 1996 and 31 December 2006, or for the period 2007 through 2010 in one of 13 hospitals in the new Region of Southern Denmark (including Funen). The extension of the area was due to a change in the organisation of the health care system in 2007, including a structural change from 14 counties to five regions. Women with concomitant or prior surgery for pelvic organ prolapse were included. Women younger than 18 years were excluded.

### *Data sources*

Data for this study were retrieved from three Danish registers: the NPR, Odense University Pharmacoepidemiologic Database (OPED), the Statistics Denmark. All Danish citizens are assigned a unique Civil Registration Number (CRN), which enables individual-level linkage across registries (19).

The NPR contains data on discharges from public hospitals in Denmark, and the completeness of recordings has been estimated to be 99.4% (20). Information available in the registry is the CRN, the dates of admission, date of discharge, and discharge diagnoses, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (21,22) as well as codes from the Danish classification system of surgical procedures (23).

Information on relevant drugs (antibiotics, and oestrogens) was retrieved from the OPED in the period 1995 to 2011 for the entire study population.

1  
2  
3  
4 The OPED is pharmacy-based and captures all reimbursed prescriptions, and contains person-  
5  
6 identifiable data with complete coverage on all computerized prescription reimbursements from the  
7  
8 County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended  
9  
10 to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution  
11  
12 of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and  
13  
14 the prescribing of drugs is very similar to the national average (24).

15  
16  
17 Prescription reimbursements are given independently of patient income to all legal inhabitants of  
18  
19 Denmark as a part of the National Health Service. Each record includes the CRN, the date of  
20  
21 purchase, a full account of what have been dispensed, including the brand name, and the  
22  
23 Anatomical Therapeutic Chemical (ATC) classification code. Information not included in the  
24  
25 prescription database is drugs sold over the counter or drugs not reimbursed by the county authority  
26  
27 (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level  
28  
29 and annual income were retrieved from the Danish Integrated Database for Labor Market Research  
30  
31 at Statistics Denmark, a database with annually updated socioeconomic data for each Danish  
32  
33 citizen, mainly supplied by tax authorities, educational institutions, and employment services (25).  
34  
35  
36  
37  
38

#### 39 *Antibiotics under study*

40  
41 Included drugs were antibiotics traditionally used in Denmark exclusively or predominantly for the  
42  
43 treatment of UTI (Sulfamethizole [ATC J01EB02], Pivmecillinam [ATC J01CA08], Nitrofurantoin  
44  
45 [ATC J01XE01], Trimethoprim [ATC J01EA01], as well as Mecillinam [ATC J01CA11]) (26,27),  
46  
47 and with a duration of 3-5 days. The indications for the prescribed drugs are not registered in the  
48  
49 OPED; therefore pivampicillin and amoxicillin were not included – as these antibiotics are also  
50  
51 commonly used in treatment of upper respiratory tract infections as well. Likewise, broader  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 spectrum antibiotics such as cephalosporins and quinolones were not included, as they are not  
5  
6 commonly used for UTIs in Denmark.  
7  
8  
9

#### 10 *Exposed and unexposed cohorts*

11  
12 Exposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between 1  
13  
14 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and  
15  
16 having redeemed one or more prescriptions on antibiotics within 365 days preceding the date of  
17  
18 surgery (index date).  
19  
20

21  
22 Unexposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between  
23  
24 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark  
25  
26 without having redeemed similar prescriptions within the same time frame.  
27  
28  
29

#### 30 *Outcome data*

31  
32 For both exposed and unexposed women, the outcome was use of antibiotics for UTI, defined as  
33  
34 having redeemed at least one prescription for these antibiotics within 1) 60 days after the index date  
35  
36 (short term postoperative users), and 2) 61 days to 365 days after the index date (long term  
37  
38 postoperative users). These outcomes were not mutually exclusive, i.e. a woman might be classified  
39  
40 both as a short and long term user postoperatively.  
41  
42  
43  
44  
45

#### 46 *Covariates*

47  
48 The use of antibiotics might be affected by age, type of surgery, use of oestrogen, comorbidity,  
49  
50 calendar time, and the individuals' ability to pay for the medicine might be affected by educational  
51  
52 level, and annual income. Therefore, these variables were included in the analysis as potential  
53  
54 confounders.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 *Type of procedures:* The types of UI surgery were divided into four groups according to the surgical  
5  
6 procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-  
7  
8 urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types  
9  
10 of UI surgeries.

11  
12 *Oestrogen:* Use of oestrogens [ATC G03C] was included in the analyses as a confounder.

13  
14 To adjust for preoperative oestrogen use, preoperative users of oestrogens were defined as women  
15  
16 who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and  
17  
18 non-users were defined as those who had no preoperative oestrogen use during the same period.  
19  
20

21 Both local and systemic oestrogens were included.

22  
23 *Comorbidity:* The comorbidity was classified according to the validated, well-known and widely  
24  
25 used Charlson comorbidity index (CCI) (28–31), which assigns different weights (1, 2, 3, and 6) to  
26  
27 20 different disease categories specified by medical condition and severity (for example, diabetes,  
28  
29 cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). The CCI  
30  
31 was computed based on each woman's complete hospital discharge history from the NPR since  
32  
33 1977. A categorised version of the CCI score values was used: 0 (low), 1-2 (medium) and 3+ (high)  
34  
35 (32).  
36  
37

38  
39 *Education and income:* Information on educational level and annual income for each woman was  
40  
41 retrieved as a measure of socioeconomic status. Educational level was categorised according to the  
42  
43 highest attained educational level in the year of surgery: "Basic" (basic school/high school  
44  
45 education: 7-12 years of primary, secondary and grammar-school education), "Secondary"  
46  
47 (vocational education, 10-12 years of education), and "Higher" (a university degree or an  
48  
49 examination in another higher institution requiring an average total of 13 years or more) (28).  
50  
51

52 On the basis of quartiles of annual income for each woman in the year of her surgery, we  
53  
54 categorised women in low (  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 1<sup>st</sup> quartile), medium (2<sup>nd</sup> and 3<sup>rd</sup> quartile), and high income (4<sup>th</sup> quartile).  
7  
8  
9

### 10 *Statistical analysis*

11  
12 The use of antibiotics for UTI within the first 365 days after surgery for exposed and unexposed  
13 cohorts was illustrated in a flowchart. We also constructed contingency tables for the main study  
14 variables, and computed odds ratios (ORs), with 95% confidence intervals (CI).  
15  
16  
17

18  
19 To analyse the significance of preoperative antibiotic use as risk factor of postoperative use (within  
20 60 days and within 61-365 days after surgery), adjusted ORs were estimated by means of  
21 multivariate logistic regression models.  
22  
23

24  
25 Adjustment was made for age (18-39, 40-59, and  $\geq 60$  years (reference)), type of procedures  
26 (toMUS (reference), rpMUS, bulking, others), education (basic (reference), secondary, higher),  
27  
28 annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+),  
29  
30  
31  
32  
33  
34  
35  
36 calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365  
37 days preceding surgery (No (reference), yes).

38  
39 Stratified analyses were performed according to use of oestrogens before surgery to examine the  
40 association between the use of antibiotics for UTI in oestrogen users vs. oestrogen non-users.  
41

42 All analyses were performed using Stata Release 12.0.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010; 2,073 had a solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse.

Of the 2,151 women, a total of 1,655 (76.9%) women did not use antibiotics for UTI within 365 days prior to surgery, while 496 (23.1%) did, and the majority (376/496=75.8%) redeemed  $\leq 2$  prescriptions preoperatively, and only a minority (42/496=8%) redeemed more than five or more prescriptions. The use of antibiotics for UTI within 365 days after surgery is detailed for the exposed and unexposed cohorts in Figure 1. The most commonly used antibiotics both preoperatively and postoperatively were Sulfamethizol and Pivmecillinam.

### *Women having redeemed prescriptions for antibiotics for UTI before surgery (exposed)*

Of the 496 women with prior use of antibiotics for UTI, 129 (26.0%) redeemed a prescription for antibiotics for UTI within 0-60 days after surgery, and of these, 85 (65.9%) also within 61-365 days after surgery (Figure 1). A total of 215 (43.3%) continued to redeem prescriptions for antibiotics within 61-365 days (Figure 1).

### *Women with no usage of antibiotics for UTI before surgery (unexposed)*

Out of the 1,655 women who did not redeem prescription before surgery, 182 (11.0%) women had a short term use of antibiotics for UTI after surgery; and of these, 64 women were also long term users (Figure 1). Among unexposed without short term postoperative use of antibiotics, 171 (10.3%) became long term postoperative user (Figure 1). The total of women with long term antibiotic use was 235 (14.2%).

### *Comparison of exposed and unexposed cohorts*

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedure was toMUS accounting for approximately half of the procedures performed in both the exposed and the unexposed group. The most commonly prescribed drugs prior to surgery were sulfamethizol and pivmecillinam. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, and to have higher comorbidity indices. There was no difference in educational level or personal annual income.

The unadjusted OR of a prior antibiotic user being a postoperative user short and long term was 2.8 (95% CI 2.2-3.7), and 4.6 (95% CI 3.7-5.8), respectively. The adjusted OR of being short and long term user of antibiotics for UTI after surgery was 2.6 (95% CI 2.0-3.5), and 4.5 (95% CI 3.5-5.7), respectively (Table 2). Thus, adjustment for confounders did virtually not change the relative risk estimates. The details from logistic regression models are presented in Table 2 showing the impact of each prognostic factor included. Regarding short term use the strongest risk factors were procedure types (rpMUS/others), high comorbidity index, and preoperative antibiotic use.

Preoperative use of antibiotics for UTI was the strongest risk factor of long term postoperative use.

Stratified analyses according to the use of oestrogens before surgery showed that among users of oestrogen, the adjusted OR for short and long term use of antibiotics for UTI after surgery increased to 3.3 (95% CI 2.3-4.8) and 5.2 (95% CI 3.7-7.3), respectively, Table 3.

## Discussion

Among 2,151 women undergoing surgery for UI nearly one fourth had redeemed at least one prescription of antibiotics for UTI preoperatively, and among preoperative users nearly half of the women also redeemed prescriptions of antibiotics for UTI within 61-365 days after surgery. Among preoperative users of antibiotics we found a 2-3 fold increased risk of short term use of antibiotics for UTI after surgery, and a 4-5 fold increased risk of being long term user. In women not using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics after surgery. To ensure that our results were not influenced by effect modification of oestrogen use we stratified our analyses for preoperative use of oestrogen. In both strata we found an increased risk of postoperative antibiotic use for the exposed women. The risk estimates for short- and long term use were, however, higher among women using oestrogen preoperatively compared to women without prior oestrogen use.

The proportion of women with concomitant surgery for pelvic organ prolapse in our cohort of women with UI surgery was low, and this was as expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (34). Thus, our results were not influenced by a mixed cohort with both UI surgery and pelvic organ prolapse surgery.

Our study has several strengths: 1) it is population-based in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) the source of procedure codes in the NPR has high coverage and validity - The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a high quality of the data with positive predictive values of 94-100% (35-37), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (24), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in

1  
2  
3  
4 the follow up period for all included women, 6) outcome data on postoperative antibiotic  
5 prescriptions are recorded independently of prior antibiotic use, thus preventing differential  
6 misclassification of the outcome, 7) the antibiotics included in this study are UTI specific and are  
7 drugs of choice in Denmark for treating UTI, and finally 8) the surgical procedures included have  
8 no other indications than UI, which strongly limits the number of alternative interpretations of our  
9 findings. Furthermore, the exclusion of antibiotics with other indications than UTI may even have  
10 led to an underestimation of the risk of UTI.

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
There are possible limitations to our study. We have no information on perioperative use of  
antibiotic, antibiotic given while the patient was still hospitalised, or results of urine culture. A  
redeemed prescription of antibiotics for UTI does not necessarily equal a UTI, and urine culture is  
not always performed prior to a prescription. Thus, empiric therapy is possible. To prevent UTI and  
other postoperative infections a perioperative single-dose of intravenous antibiotic is often used in  
Denmark (38). However, perioperative antibiotic use is unlikely to be much different between  
exposed and unexposed cohorts and will thus not bias our relative risk estimates. In the short term  
perspective after surgery we had no knowledge of postoperative catheter usage which is a  
limitation, especially since postoperative UTI is associated with catheter usage in the postoperative  
period (39), but again we have no reasons to believe that use of catheters differed among exposed  
and unexposed cohorts. We were not able to control for all potential confounders such as body mass  
index, parity, intraoperative bladder perforation, or precise menopausal status, but the importance of  
these factors for the association examined in this study is not clear. We had no data on patient  
symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome  
were predominant, or on urodynamic study, and it could have been interesting to further examine  
the users of UTI antibiotics (both before and after surgery) according to the type of UI  
symptomatology.

1  
2  
3  
4 It is surprising that among women having use of antibiotics for UTIs before UI surgery, half of  
5  
6 them have a continuing tendency to use of these antibiotics after surgery. This is not explained by  
7  
8 recurrent UI surgery in the study period of one year after surgery as only approximately 5% of the  
9  
10 women experienced a new surgery in our population. Possible explanations for the continuing  
11  
12 tendency to UTI could be a genetic predisposition for UTI, an anatomic predisposition for UTI, or  
13  
14 an increased awareness of UTI for both the women and their doctor.

15  
16  
17 Based on the flowchart in our study, we found a tendency to continuing UTI among women with  
18  
19 preoperative antibiotic use in both short- and long term postoperatively. To our knowledge, this is  
20  
21 the largest, and only population-based, study examining the use of antibiotics for UTI in relation to  
22  
23 surgery for UI and addressing the risk of both short- and long term postoperative use of antibiotics  
24  
25 for UTI among women with preoperative UTI. In addition, our study provides knowledge about  
26  
27 which other factors than preoperative antibiotic were important for postoperative antibiotic use for  
28  
29 UTI. We found that for short term use procedure type (rpMUS, others), and high comorbidity were  
30  
31 risk factors, and for long term use high comorbidity was a risk factor. Our study also showed that  
32  
33 educational level and personal income did not seem to influence the risk of postoperative antibiotic  
34  
35 use.  
36  
37  
38

39  
40 In Denmark, dipstick urine test is a part of the preoperative examination, and surgeons might feel  
41  
42 encouraged to treat the women with antibiotics prior to surgery based on dipstick urine test without  
43  
44 symptoms or urine culture in an attempt to try to minimize the risk of postoperative UTI.

45  
46 According to the Danish Programme for surveillance of antimicrobial consumption and resistance  
47  
48 in bacteria from animals, food and humans, the resistance, especially in bacterias other than  
49  
50 *Escherichia coli*, has increased during the last years. *Escherichia coli* is the most frequent cause of  
51  
52 UTIs both in community and hospital-acquired UTIs.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 Our study calls for further studies within this area – studies examining UTI before and after surgery  
5  
6 according to different types of UI (stress UI, urgency UI, mixed UI), UTI in relation to surgery in  
7  
8 especially post-menopausal women, issues regarding recurrent UTI and UI surgery, and if  
9  
10 prophylactic antibiotic use (perioperative intravenous/prolonged oral antibiotics) could reduce the  
11  
12 risk of postoperative UTI after UI surgery in a short- and long term perspective. Furthermore, it  
13  
14 would be interesting to assess the use of similar antibiotics in the background population of women  
15  
16 to examine whether there is an increased antibiotic burden associated with surgery for UI.  
17  
18 In conclusion, we found that one in four women undergoing surgery for UI was treated for UTI  
19  
20 before surgery, and half of these women continued the tendency of UTI after surgery. In women not  
21  
22 using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI  
23  
24 after surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of  
25  
26 these antibiotics before surgery.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 **Acknowledgement:**None  
5

6  
7 **Funding:** This study was funded by 1) Nordic Urogynaecology Association (NUGA) Research  
8  
9 Grant 2) A. P. Møller and Chastine Mc-Kinney Møller Foundation for General Purposes 3) Center  
10  
11 for Clinical Epidemiology, Odense University Hospital, and 4) Region of Southern Denmark  
12  
13

14  
15 **Financial disclaimer/Conflicts of interest:** None  
16

17  
18  
19 **Contributors:**All authors have drafted the article, revised it critically for important intellectual  
20  
21 content, and approved the finale version to be published. All authors are responsible for the study  
22  
23 concept and design, and participated in the interpretation of data. RG is the guarantor and has full  
24  
25 access to all of the data in the study.  
26  
27

28  
29 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at  
30  
31 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
32  
33 work; no financial relationships with any organisations that might have an interest in the submitted  
34  
35 work in the previous three years.  
36  
37

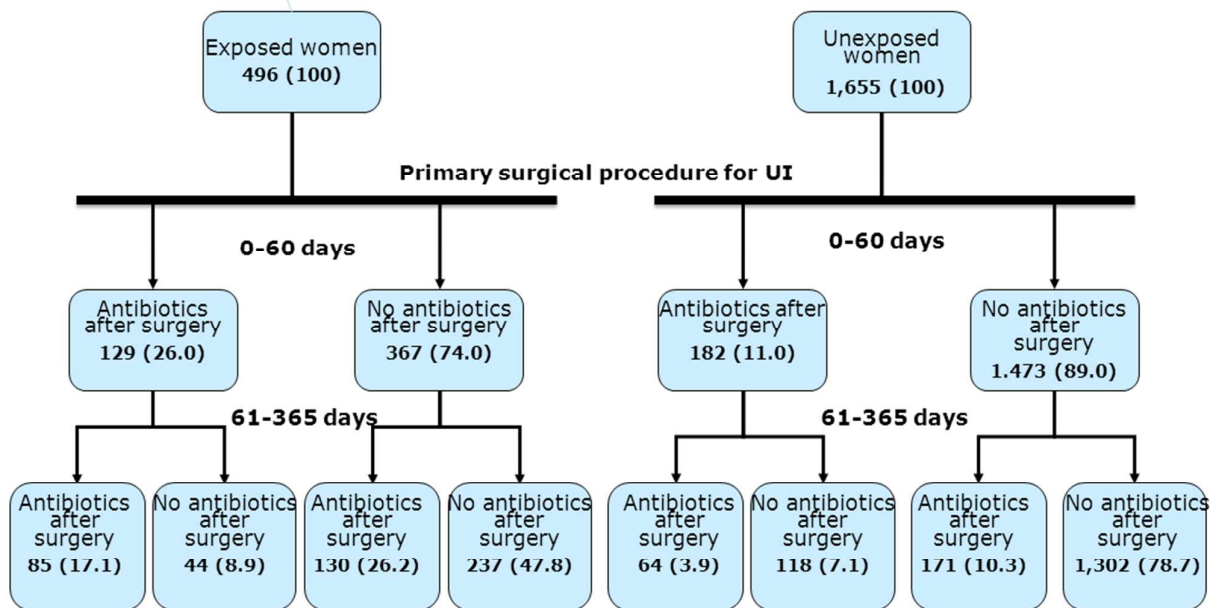
38  
39 **Data sharing:** According to the Danish Data Protection Agency, we are not allowed to share our  
40  
41 data from the Danish National Patient Registry. This would require a special approval from both the  
42  
43 Danish Data Protection Agency and the Statens Serum Institut who provides the data from the  
44  
45 Danish National Patient Registry.  
46  
47

48  
49  
50  
51 **Ethical approval** The study was approved by the Danish Data Protection Agency (no. 2009-41-  
52  
53 3564). According to Danish law, ethical review board approval or patient consent are not required  
54  
55 for register-based studies.  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 **Copyright** The Corresponding Author has the right to grant on behalf of all authors and does  
8  
9 grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity,  
10  
11 in all forms, formats and media (whether known now or created in the future), to i) publish,  
12  
13 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other  
14  
15 languages, create adaptations, reprints, include within collections and create summaries, extracts  
16  
17 and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the  
18  
19 Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic  
20  
21 links from the Contribution to third party material where-ever it may be located; and, vi) licence  
22  
23 any third party to do any or all of the above.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



**Figure 1** Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery. Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.



**Table 1** Baseline characteristics of all included women (N=2,151) having a primary surgical procedure for UI in Denmark, 1996-2010.

	Exposed <sup>a</sup> n=496	Unexposed <sup>b</sup> n=1,655
Mean age (±SD), years		
(At time of first UI surgery)	60.2 (±13.2)	54.2 (±12.4)
Age groups n (%)		
18-39	30 (6.1)	182 (11.0)
40-59	196 (39.5)	911 (55.1)
60-	270 (54.4)	562 (33.9)
Procedures n (%)		
rpMUS	140 (28.2)	535 (32.3)
toMUS	222 (44.8)	750 (45.3)
Bulking	110 (22.2)	250 (15.1)
Others	24 (4.8)	120 (7.3)
Concomitant prolapse surgery n (%)	12 (2.4)	66 (4.0)
Antibiotics before surgery n (%) <sup>c</sup>		
Sulfamethizol - J01EB02	299 (60.3)	-
Pivmecillinam - J01CA08	288 (58.1)	-
Nitrofurantoin - J01XE01	65 (13.1)	-
Trimethoprim - J01EA01	45 (9.1)	-

Mecillinam - J01CA11	0 (0)	-
Oestrogen users n (%)**		
No	211 (42.5)	997 (60.2)
Yes	285 (57.5)	658 (39.8)
Comorbidity (CCI) n (%)		
0	298 (60.1)	1,214 (73.4)
1-2	139 (28.0)	381 (23.0)
3+	59 (11.9)	60 (3.6)
Educational level n (%)***		
Basic	229 (47.4)	688 (42.3)
Secondary	170 (35.2)	600 (36.8)
Higher	84 (17.4)	340 (20.9)
Annual income n (%)		
Low (1 <sup>st</sup> quartile)	152 (30.7)	385 (23.3)
Middle (2 <sup>nd</sup> -3 <sup>rd</sup> quartile)	252 (50.8)	825 (49.9)
High (4 <sup>th</sup> quartile)	92 (18.5)	445 (26.9)
Year of surgery n (%)		
1996-2006	106 (21.4)	353 (21.3)
2007-2008	186 (37.5)	605 (36.6)
2009-2010	204 (41.1)	697 (42.1)

<sup>a</sup>Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery.

<sup>b</sup>Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.

\*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.

\*\*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

\*\*\*Unknown highest attained educational level: 40 women

Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 2** Risk factors of postoperative use of antibiotics. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii), long term (61-356 days after surgery)

	Post op non-use	Post op short term use		Post op non-use	Post op long term use	
	Number	Number	OR (95% CI)	Number	Number	OR (95% CI)
Preoperative use						
No	1,473	182	Reference	1,420	235	reference
Yes	367	129	2.6 (2.0-3.5)	281	215	4.5 (3.5-5.7)
Age group						
18-39	185	27	0.9 (0.5-1.5)	163	49	1.5 (0.9-2.3)
40-59	981	126	0.6 (0.5-0.9)	931	176	0.7 (0.5-0.9)
60+	674	158	Reference	607	225	reference
Procedure						
rpMUS	568	107	1.7 (1.1-2.7)	529	146	1.3 (0.9-1.9)
toMUS	849	123	Reference	782	190	reference
Bulking	315	45	1.4 (0.9-2.0)	278	82	1.1 (0.8-1.5)
Others	108	36	3.1 (1.6-5.9)	112	32	1.5 (0.8-2.8)
Preoperative use of oestrogen*						
No	1,059	149	Reference	992	216	reference
Yes	781	162	1.2 (0.9-1.6)	709	234	1.2 (0.9-1.5)
Comorbidity (CCI)						
0	1,328	184	Reference	1,241	271	reference
1-2	425	95	1.5 (1.1-2.0)	384	136	1.4 (1.1-1.8)
3+	87	32	3.1 (1.6-5.9)	76	43	1.5 (1.0-2.4)
Educational level**						
Basic	775	142	Reference	702	215	reference
Secondary	665	105	1.1 (0.8-1.5)	623	147	1.0 (0.7-1.1)
Higher	362	62	1.3 (0.9-2.0)	342	82	0.9 (0.6-1.3)
Annual income						
Low	434	103	Reference	404	133	reference
Middle	930	147	0.9 (0.6-1.2)	847	230	1.0 (0.8-1.3)
High	476	61	0.9 (0.6-1.4)	450	87	0.9 (0.6-1.3)
Year of surgery						
1996-2006	363	96	1.4 (0.9-2.2)	352	107	0.9 (0.7-1.1)
2007-2008	692	99	Reference	628	163	reference
2009-2010	785	116	1.0 (0.8-1.4)	721	180	1.0 (0.8-1.4)

\*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

\*\*Unknown highest attained educational level: 40 women

Abbreviations: Post op=postoperative, OR = odds ratio, CI = confidence interval , rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 3** Stratified analyses according to use of oestrogen before surgery for UI to examine the association between preoperative use of antibiotics for urinary tract infection and postoperative use.

Preop.	Preop.	Crude OR (95% CI)	Adj. OR* (95% CI)	Crude OR (95% CI)	Adj. OR* (95% CI)
oestrogen n	antibiotics n	Short term	Short term	Long term	Long term
Yes 943	Yes 285	3.5 (2.5-5.0)	3.3 (2.3-4.8)	5.2 (3.8-7.2)	5.2 (3.7-7.3)
	No 658				
No 1.208	Yes 211	2.0 (1.3-2.9)	2.0 (1.3-3.0)	3.8 (2.7-5.2)	3.7 (2.6-5.3)
	No 997				

\*Adjusted for age, procedure type, comorbidity, educational level, annual income, and calendar year of surgery.  
Abbreviations: Preop. = preoperative, Adj. = adjusted, OR = odds ratio, CI = confidence interval

## References

1. Foxman B. Recurring urinary tract infection: incidence and risk factors. *Am J Public Health* 1990;80:331–3.
2. Athanasiou S, Anstaklis A, Betsi GI, et al. Clinical and urodynamic parameters associated with history of urinary tract infections in women. *Acta Obstet Gynecol Scand* 2007;86:1130–5.
3. Hu KK, Boyko EJ, Scholes D, et al. Risk factors for urinary tract infections in postmenopausal women. *Archives of internal medicine* 2004;164:989–93.
4. Raz R, Gennesin Y, Wasser J, et al. Recurrent urinary tract infections in postmenopausal women. *Clin Infec Diseases* 2000;30:152–6.
5. Bodhare TN, Valsangkar S, Bele SD. An epidemiological study of urinary incontinence and its impact on quality of life among women aged 35 years and above in a rural area. *Indian IJU* 2010;26:353–8.
6. Fok CS, McKinley K, Mueller ER, et al. Day of surgery urine cultures identify urogynecologic patients at increased risk for postoperative urinary tract infection. *J Urol* 2013;189:1721–4.
7. Sutkin G, Alperin M, Meyn L, et al. Symptomatic urinary tract infections after surgery for prolapse and/or incontinence. *Int Urogynecol J* 2010;21:955–61.
8. Nygaard I, Brubaker L, Chai TC, et al. Risk factors for urinary tract infection following incontinence surgery. *Int Urogynecol J* 2011;22:1255–65.
9. Ingber MS, Vasavada SP, Firoozi F, et al. Incidence of perioperative urinary tract infection after single-dose antibiotic therapy for midurethral slings. *Urol* 2010;76:830–4.
10. Jackson D, Higgins E, Bracken J, et al. Antibiotic Prophylaxis for Urinary Tract Infection After Midurethral Sling: A Randomized Controlled Trial. *Fem Pelv Med & Reconstrc Surgery* 2013;19:137–41.
11. Anger J, Litwin M, Wang Q, et al. Complications of sling surgery among female Medicare beneficiaries. *Obstet Gynecol* 2007;109:707–14.
12. Stanford EJ, Paraiso MFR. A comprehensive review of suburethral sling procedure complications. *J Minimally Inv Gynecology* 1999;15:132–45.
13. LaSala C a, Schimpf MO, Udoh E, et al. Outcome of tension-free vaginal tape procedure when complicated by intraoperative cystotomy. *Am J Obstet Gynecol* 2006;195:1857–61.
14. Pugsley H, Barbrook C, Mayne CJ, t al. Morbidity of incontinence surgery in women over 70 years old: a retrospective cohort study. *BJOG* 2005;112:786–90.

15. Ward K, Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002;325:67.
16. Tamussino K, Hanzal E, Kolle D, et al. Tension-free vaginal tape operation: results of the Austrian registry. *Obstet Gynecol* 2001;98:732–6.
17. Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association ( IUGA )/ International Continence Society ( ICS ) Joint Terminology and Classification of the Complications Related Directly to the Insertion of Prostheses ( Meshes , Implants , Tapes ) and Grafts in Female P. *Int Urogynecol J* 2011;22:3-15.
18. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–5.
20. Andersen T, Madsen M, Jørgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:262–8.
21. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-8). Geneva, Switzerland; 1967.
22. World Health Organization. International Classification of Diseases - 10th revision (ICD-10) [Internet]. 2013. Available from: <http://www.who.int/classifications/ics/en/>
23. Nordic Medico-Statistical Committee. Classification of Surgical Procedures, version 1.15. 2010 no. 93.
24. Gaist D, Sørensen H, Hallas J. The Danish Prescription Registers. *Dan Med Bull*. 1997;44:445–8.
25. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011;39:95–8.
26. Bjerrum L, Grindsted P. How to treat uncomplicated cystitis? *Ugeskr Laeger*. 2000;162:197–8 [Danish].
27. Bjerrum L, Dessau R, Hallas J. Treatment failures after antibiotic therapy of uncomplicated urinary tract infections. A prescription study. *Scand J Primary Health Care*. 2002;20:97–101.
28. Dalton SO, Steding-Jessen M, Engholm G, et al. Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 2008;44:1989–95.
29. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–83.

- 1  
2  
3  
4 30. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies  
5 using administrative databases. *Int J Epidemiol* 2000;29:891–8.  
6  
7 31. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10  
8 diagnostic coding used to assess Charlson comorbidity index conditions in the population-  
9 based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.  
10  
11 32. Thomsen R, Riis A, Christensen S, et al. Diabetes and 30-Day Mortality From A Danish  
12 population-based cohort study. *Diabetes Care*. 2006;29:805–10.  
13  
14 33. Svenningsen R, Borstad E, Spydslaug AE, et al. Occult incontinence as predictor for  
15 postoperative stress urinary incontinence following pelvic organ prolapse surgery. *Int*  
16 *Urogynecol J* 2012;23:843–9.  
17  
18 34. Andersen T, Madsen M, Loft A. Validity of surgical information from the Danish National  
19 Patient Registry with special attention to the analysis of regional variations in hysterectomy  
20 rates. *Ugeskr Laeger* 1987;149:2420–2 [Danish].  
21  
22 35. Mosbech J, Jørgensen J, Madsen M, et al. The national patient registry. Evaluation of data  
23 quality. *Ugeskr Laeger* 1995;157:3741–5 [Danish].  
24  
25 36. Ottesen M. Validity of the registration and reporting of vaginal prolapse surgery. *Ugeskr*  
26 *Laeger* 2009;171:404–8 [Danish].  
27  
28 37. Guldberg R, Brostrøm S, Hansen JK, et al. The Danish Urogynaecological Database:  
29 establishment, completeness and validity. *Int Urogynecol J* 2013;24:983–90.  
30  
31 38. Wald H, Ma A, Bratzler D, et al. Indwelling Urinary Catheter Use in the Postoperative  
32 Period. *Arch Sur*. 2008;143:551–7.  
33  
34 39. Platt R, Polk B, Murdock B, et al. Risk factors for nosocomial urinary tract infection. *Am J*  
35 *of Epidemiol*. 1986;124:977–85.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Title page

# Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence – a cohort study

Rikke Guldberg<sup>1,2</sup>, Ulrik Schiøler Kesmodel<sup>3</sup>, Søren Brostrøm<sup>4</sup>, Linda Kærlev<sup>1,2</sup>, Jesper Kjær Hansen<sup>1,2</sup>, Jesper Hallas<sup>5</sup>, Bente Mertz Nørgård<sup>1,2</sup>

<sup>1</sup>Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

<sup>2</sup>Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

<sup>3</sup>Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark

<sup>4</sup>Department of Hospital Services and Emergency Management, Danish Health and Medicines Authority, Copenhagen, Denmark

<sup>5</sup>Research Unit of Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark

## Corresponding author

Rikke Guldberg, Center for Clinical Epidemiology, Odense University Hospital, Sdr. Boulevard 29, entrance 101, 4<sup>th</sup>, 5000 Odense C, Denmark.

Mail: [Rikke.Guldberg.Soerensen@rsyd.dk](mailto:Rikke.Guldberg.Soerensen@rsyd.dk)

Phone: +45 3070 3692

Fax: +45 6591 7264

**Keywords:** antibiotics, clinical epidemiology, surgery, urinary incontinence, urinary tract infection

**Word counts:** 3.044



## Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CRN = Civil Registration Number

ICD = International Classification of Diseases

MUS = mid-urethral sling

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

UTI = Urinary tract infection

## Abstract

**Objective** To describe the use of antibiotics for urinary tract infection (UTI) before and after surgery for urinary incontinence (UI); and for those with use of antibiotics before surgery, to estimate the risk of treatment for a postoperative UTI, relative to those without use of antibiotics before surgery.

**Design** A historical population-based cohort study

**Setting** Denmark

**Participants** Women (age $\geq$ 18 years) with a primary surgical procedure for UI from the county of Funen and the Region of Southern Denmark from 1996 throughout 2010. Data on redeemed prescriptions of antibiotics +/- 365 days from the date of surgery were extracted from a prescription database.

**Main outcome measures** Use of antibiotics for UTI in relation to UI surgery, and the risk of being a postoperative user of antibiotics for UTI among preoperative users.

**Results** A total of 2,151 women had a primary surgical procedure for UI; of these 496 (23.1%) were preoperative users of antibiotics for UTI. Among preoperative users, 129 (26.0%) and 215 (43.3%) also redeemed prescriptions of antibiotics for UTI within 0-60 and 61-365 days after surgery, respectively. Among preoperative non-users, 182 (11.0%) and 235 (14.2%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antibiotics for UTI was a strong risk factor for postoperative treatment for UTI, both within 0-60 days [OR, adjusted = 2.6 (95% confidence interval (CI) 2.0-3.5)] and within 61-365 days [OR, adjusted = 4.5 (95% CI 3.5-5.7)].

**Conclusions** One in four women undergoing surgery for UI was treated for UTI before surgery, and half of them had a continuing tendency to UTIs after surgery. Use of antibiotics for UTI before

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

surgery was a strong risk factor for antibiotic use after surgery. In women not using antibiotics for UTI before surgery only a minor proportion initiated use after surgery.

For peer review only

## Introduction

Urinary tract infection (UTI) is a common problem in women, and 40% of women will have a UTI during life-time – and of these 27% will have recurrent UTI within 12 months (1). There are several risk factors for UTI and recurrent UTI; e.g. high age, urogenital atrophy, and urinary incontinence (UI) (2,3). UI is associated with UTI (2,4), and UTI might be regarded as a comorbid condition in women with UI due to a number of factors including poor perineal hygiene (5). Thus, it is not surprising that UTI is seen in women with UI, but no studies have so far examined the burden of UTI in women undergoing surgery for UI in a population based setting.

It is also well known that UTI is common after UI surgery. Risk factors of postoperative UTI include previous recurrent UTI, postoperative catheterization, positive urine cultures at day of surgery, and preoperative postvoid residual (6–9). UTI after UI surgery might occur among 6-38.34% of the women - depending on diagnostic methods and criteria (8,10–16), and surgery related infections occur within 2 months (17). Thus, while some knowledge of UTI exists in the short term perspective after UI surgery, there is only little evidence on the frequency of UTI in a more long term perspective after UI surgery (8).

The purpose of this study was to examine the use of antibiotics for UTI before and after surgery for UI, and among women using antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term perspective. This topic is highly clinical relevant in the counselling of women prior to surgery for UI: What can they expect of postoperative complications? Can preoperative drug users expect to continue drug use after surgery?

## Materials and Methods

### *Study population and settings*

Women were included in the study if they had a primary surgical procedure for UI within the period of 1 January 1996 through 31 December 2010. Data on performed procedures were retrieved from the Danish National Patient Registry (NPR) (18) according to codes listed in Appendix 1. The surgical procedures were performed in one of four hospitals in the county of Funen, Denmark, between 1 January 1996 and 31 December 2006, or for the period 2007 through 2010 in one of 13 hospitals in the new Region of Southern Denmark (including Funen). The extension of the area was due to a change in the organisation of the health care system in 2007, including a structural change from 14 counties to five regions. Women with concomitant or prior surgery for pelvic organ prolapse were included. Women younger than 18 years were excluded.

### *Data sources*

Data for this study were retrieved from three Danish registers: the NPR, Odense University Pharmacoepidemiologic Database (OPED), the Statistics Denmark. All Danish citizens are assigned a unique Civil Registration Number (CRN), which enables individual-level linkage across registries (19).

The NPR contains data on discharges from public hospitals in Denmark, and the completeness of recordings has been estimated to be 99.4% (20). Information available in the registry is the CRN, the dates of admission, date of discharge, and discharge diagnoses, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (21,22) as well as codes from the Danish classification system of surgical procedures (23).

Information on relevant drugs (antibiotics, and oestrogens) was retrieved from the OPED in the period 1995 to 2011 for the entire study population.

1  
2  
3  
4 The OPED is pharmacy-based and captures all reimbursed prescriptions, and contains person-  
5  
6 identifiable data with complete coverage on all computerized prescription reimbursements from the  
7  
8 County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended  
9  
10 to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution  
11  
12 of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and  
13  
14 the prescribing of drugs is very similar to the national average (24).

15  
16  
17 Prescription reimbursements are given independently of patient income to all legal inhabitants of  
18  
19 Denmark as a part of the National Health Service. Each record includes the CRN, the date of  
20  
21 purchase, a full account of what have been dispensed, including the brand name, and the  
22  
23 Anatomical Therapeutic Chemical (ATC) classification code. Information not included in the  
24  
25 prescription database is drugs sold over the counter or drugs not reimbursed by the county authority  
26  
27 (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level  
28  
29 and annual income were retrieved from the Danish Integrated Database for Labor Market Research  
30  
31 at Statistics Denmark, a database with annually updated socioeconomic data for each Danish  
32  
33 citizen, mainly supplied by tax authorities, educational institutions, and employment services (25).  
34  
35  
36  
37  
38  
39

#### 40 *Antibiotics under study*

41  
42 Included drugs were antibiotics traditionally used in Denmark exclusively or predominantly for the  
43  
44 treatment of UTI (Sulfamethizole [ATC J01EB02], Pivmecillinam [ATC J01CA08], Nitrofurantoin  
45  
46 [ATC J01XE01], Trimethoprim [ATC J01EA01], as well as Mecillinam [ATC J01CA11]) (26,27).  
47  
48 and with a duration of 3-5 days.—The indications for the prescribed drugs are not registered in the  
49  
50 OPED; therefore pivampicillin and amoxicillin were not included – as these antibiotics are also  
51  
52 commonly used in treatment of upper respiratory tract infections as well. Likewise, broader  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 spectrum antibiotics such as cephalosporins and quinolones were not included, as they are not  
5  
6 commonly used for UTIs in Denmark.  
7  
8  
9

#### 10 *Exposed and unexposed cohorts*

11  
12 Exposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between 1  
13  
14 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and  
15  
16 having redeemed one or more prescriptions on antibiotics within 365 days preceding the date of  
17  
18 surgery (index date).  
19  
20

21  
22 Unexposed cohort: All women  $\geq 18$  years undergoing a primary surgical procedure for UI between  
23  
24 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark  
25  
26 without having redeemed similar prescriptions within the same time frame.  
27  
28  
29

#### 30 *Outcome data*

31  
32 For both exposed and unexposed women, the outcome was use of antibiotics for UTI, defined as  
33  
34 having redeemed at least one prescription for these antibiotics within 1) 60 days after the index date  
35  
36 (short term postoperative users), and 2) 61 days to 365 days after the index date (long term  
37  
38 postoperative users). These outcomes were not mutually exclusive, i.e. a woman might be classified  
39  
40 both as a short and long term user postoperatively.  
41  
42  
43  
44  
45

#### 46 *Covariates*

47  
48 The use of antibiotics might be affected by age, type of surgery, use of oestrogen, comorbidity,  
49  
50 calendar time, and the individuals' ability to pay for the medicine might be affected by educational  
51  
52 level, and annual income. Therefore, these variables were included in the analysis as potential  
53  
54 confounders.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 *Type of procedures:* The types of UI surgery were divided into four groups according to the surgical  
5  
6 procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-  
7  
8 urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types  
9  
10 of UI surgeries.

11  
12 *Oestrogen:* Use of oestrogens [ATC G03C] was included in the analyses as a confounder.

13  
14 To adjust for preoperative oestrogen use, preoperative users of oestrogens were defined as women  
15  
16 who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and  
17  
18 non-users were defined as those who had no preoperative oestrogen use during the same period.  
19  
20

21  
22 Both local and systemic oestrogens were included.

23  
24 *Comorbidity:* The comorbidity was classified according to the validated, well-known and widely  
25  
26 used Charlson comorbidity index (CCI) (29–31), which assigns different weights (1, 2, 3, and 6) to  
27  
28 20 different disease categories specified by medical condition and severity (for example, diabetes,  
29  
30 cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). The CCI  
31  
32 was computed based on each woman's complete hospital discharge history from the NPR since  
33  
34 1977. A categorised version of the CCI score values was used: 0 (low), 1-2 (medium) and 3+ (high)  
35  
36 (32).  
37  
38

39  
40 *Education and income:* Information on educational level and annual income for each woman was  
41  
42 retrieved as a measure of socioeconomic status. Educational level was categorised according to the  
43  
44 highest attained educational level in the year of surgery: "Basic" (basic school/high school  
45  
46 education: 7-12 years of primary, secondary and grammar-school education), "Secondary"  
47  
48 (vocational education, 10-12 years of education), and "Higher" (a university degree or an  
49  
50 examination in another higher institution requiring an average total of 13 years or more) (28).  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4 On the basis of quartiles of annual income for each woman in the year of her surgery, we  
5 categorised women in low (1<sup>st</sup> quartile), medium (2<sup>nd</sup> and 3<sup>rd</sup> quartile), and high income (4<sup>th</sup>  
6 quartile).  
7  
8  
9

### 10 11 12 *Statistical analysis*

13  
14  
15 The use of antibiotics for UTI within the first 365 days after surgery for exposed and unexposed  
16 cohorts was illustrated in a flowchart. We also constructed contingency tables for the main study  
17 variables, and computed odds ratios (ORs), with 95% confidence intervals (CI).  
18  
19

20  
21 To analyse the significance of preoperative antibiotic use as risk factor of postoperative use (within  
22 60 days and within 61-365 days after surgery), adjusted ORs were estimated by means of  
23 multivariate logistic regression models.  
24  
25  
26

27  
28 Adjustment was made for age (18-39, 40-59, and  $\geq 60$  years (reference)), type of procedures  
29 (toMUS (reference), rpMUS, bulking, others), education (basic (reference), secondary, higher),  
30 annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+),  
31 calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365  
32 days preceding surgery (No (reference), yes).  
33  
34  
35  
36  
37  
38

39 Stratified analyses were performed according to use of oestrogens before surgery to examine the  
40 association between the use of antibiotics for UTI in oestrogen users vs. oestrogen non-users.  
41  
42

43 All analyses were performed using Stata Release 12.0.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010; 2,073 had a solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse.

Of the 2,151 women, a total of 1,655 (76.9%) women did not use antibiotics for UTI within ~~in~~ 365 days prior to surgery, while 496 (23.1%) did, and the majority (376/496=75.8%) redeemed  $\leq 2$  prescriptions preoperatively, and only a minority (42/496=8%) redeemed more than five or more prescriptions. The use of antibiotics for UTI within 365 days after surgery is detailed for the exposed and unexposed cohorts in Figure 1. The most commonly used antibiotics both preoperatively and postoperatively were Sulfamethizol and Pivmecillinam.

### *Women having redeemed prescriptions for antibiotics for UTI before surgery (exposed)*

Of the 496 women with prior use of antibiotics for UTI, 129 (26.0%) redeemed a prescription for antibiotics for UTI within 0-60 days after surgery, and of these, 85 (65.9%) also within 61-365 days after surgery (Figure 1). A total of 215 (43.3%) continued to redeem prescriptions for antibiotics within 61-365 days (Figure 1).

### *Women with no usage of antibiotics for UTI before surgery (unexposed)*

Out of the 1,655 women who did not redeem prescription before surgery, 182 (11.0%) women had a short term use of antibiotics for UTI after surgery; and of these, 64 women were also long term users (Figure 1). Among unexposed without short term postoperative use of antibiotics, 171 (10.3%) became long term postoperative user (Figure 1). The total of women with long term antibiotic use was 235 (14.2%).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Comparison of exposed and unexposed cohorts*

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedure was toMUS accounting for approximately half of the procedures performed in both the exposed and the unexposed group. The most commonly prescribed drugs prior to surgery were sulfamethizol and pivmecillinam. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, and to have higher comorbidity indices. There was no difference in educational level or personal annual income.

The unadjusted OR of a prior antibiotic user being a postoperative user short and long term was 2.8 (95% CI 2.2-3.7), and 4.6 (95% CI 3.7-5.8), respectively. The adjusted OR of being short and long term user of antibiotics for UTI after surgery was 2.6 (95% CI 2.0-3.5), and 4.5 (95% CI 3.5-5.7), respectively (Table 2). Thus, adjustment for confounders did virtually not change the relative risk estimates. The details from logistic regression models are presented in Table 2 showing the impact of each prognostic factor included. Regarding short term use the strongest risk factors were procedure types (rpMUS/others), high comorbidity index, and preoperative antibiotic use. Preoperative use of antibiotics for UTI was the strongest risk factor of long term postoperative use. Stratified analyses according to the use of oestrogens before surgery showed that among users of oestrogen, the adjusted OR for short and long term use of antibiotics for UTI after surgery increased to 3.3 (95% CI 2.3-4.8) and 5.2 (95% CI 3.7-7.3), respectively, Table 3.

## Discussion

Among 2,151 women undergoing surgery for UI nearly one fourth had redeemed at least one prescription of antibiotics for UTI preoperatively, and among preoperative users nearly half of the women also redeemed prescriptions of antibiotics for UTI within 61-365 days after surgery. Among preoperative users of antibiotics we found a 2-3 fold increased risk of short term use of antibiotics for UTI after surgery, and a 4-5 fold increased risk of being long term user. In women not using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics after surgery. To ensure that our results were not influenced by effect modification of oestrogen use we stratified our analyses for preoperative use of oestrogen. In both strata we found an increased risk of postoperative antibiotic use for the exposed women. The risk estimates for short- and long term use were, however, higher among women using oestrogen preoperatively compared to women without prior oestrogen use.

The proportion of women with concomitant surgery for pelvic organ prolapse in our cohort of women with UI surgery was low, and this was as expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (34). Thus, our results were not influenced by a mixed cohort with both UI surgery and pelvic organ prolapse surgery.

Our study has several strengths: 1) it is population-based in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) the source of procedure codes in the NPR has high coverage and validity - The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a high quality of the data with positive predictive values of 94-100% (35-37), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (24), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in

1  
2  
3  
4 the follow up period for all included women, 6) outcome data on postoperative antibiotic  
5 prescriptions are recorded independently of prior antibiotic use, thus preventing differential  
6 misclassification of the outcome, 7) the antibiotics included in this study are UTI specific and are  
7 drugs of choice in Denmark for treating UTI, and finally 8) the surgical procedures included have  
8 no other indications than UI, which strongly limits the number of alternative interpretations of our  
9 findings. Furthermore, the exclusion of antibiotics with other indications than UTI may even have  
10 led to an underestimation of the risk of UTI.

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22 There are possible limitations to our study. We have no information on perioperative use of  
23 antibiotic, antibiotic given while the patient was still hospitalised, or results of urine culture. A  
24 redeemed prescription of antibiotics for UTI does not necessarily equal a UTI, and urine culture is  
25 not always performed prior to a prescription. Thus, empiric therapy is possible. To prevent UTI and  
26 other postoperative infections a perioperative single-dose of intravenous antibiotic is often used in  
27 Denmark (38). However, perioperative antibiotic use is unlikely to be much different between  
28 exposed and unexposed cohorts and will thus not bias our relative risk estimates. In the short term  
29 perspective after surgery we had no knowledge of postoperative catheter usage which is a  
30 limitation, especially since postoperative UTI is associated with catheter usage in the postoperative  
31 period (39,40), but again we have no reasons to believe that use of catheters differed among  
32 exposed and unexposed cohorts. We were not able to control for all potential confounders such as  
33 body mass index, parity, intraoperative bladder perforation, or precise menopausal status, but the  
34 importance of these factors for the association examined in this study is not clear. We had no data  
35 on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder  
36 syndrome were predominant, or on urodynamic study, and it could have been interesting to further  
37 examine the users of UTI antibiotics (both before and after surgery) according to the type of UI  
38 symptomatology.

1  
2  
3  
4 It is surprising that among women having use of antibiotics for UTIs before UI surgery, half of  
5  
6 them have a continuing tendency to use of these antibiotics-UTIs after surgery. This is not explained  
7  
8 by recurrent UI surgery in the study period of one year after surgery as only approximately 5% of  
9  
10 the women experienced a new surgery in our population. Possible explanations for the continuing  
11  
12 tendency to UTI could be a genetic predisposition for UTI, an anatomic predisposition for UTI, or  
13  
14 an increased awareness of UTI for both the women and their doctor.

15  
16  
17 Based on the flowchart in our study, we found a tendency to continuing UTI among women with  
18  
19 preoperative antibiotic use in both short- and long term postoperatively. To our knowledge, this is  
20  
21 the largest, and only population-based, study examining the use of antibiotics for UTI in relation to  
22  
23 surgery for UI and addressing the risk of both short- and long term postoperative use of antibiotics  
24  
25 for UTI among women with preoperative UTI. In addition, our study provides knowledge about  
26  
27 which other factors than preoperative antibiotic were important for postoperative antibiotic use for  
28  
29 UTI. We found that for short term use procedure type (rpMUS, others), and high comorbidity were  
30  
31 risk factors, and for long term use high comorbidity was a risk factor. Our study also showed that  
32  
33 educational level and personal income did not seem to influence the risk of postoperative antibiotic  
34  
35 use.  
36  
37  
38  
39

40 In Denmark, dipstick urine test is a part of the preoperative examination, and surgeons might feel  
41  
42 encouraged to treat the women with antibiotics prior to surgery based on dipstick urine test without  
43  
44 symptoms or urine culture in an attempt to try to minimize the risk of postoperative UTI.

45  
46 According to the Danish Programme for surveillance of antimicrobial consumption and resistance  
47  
48 in bacteria from animals, food and humans, the resistance, especially in bacterias other than  
49  
50 Escherichia coli, has increased during the last years. Escherichia coli is the most frequent cause of  
51  
52 UTIs both in community and hospital-acquired UTIs.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 Our study calls for further studies within this area – studies examining UTI before and after surgery  
5  
6 according to different types of UI (stress UI, urgency UI, mixed UI), UTI in relation to surgery in  
7  
8 especially post-menopausal women, issues regarding recurrent UTI and UI surgery, and if  
9  
10 prophylactic antibiotic use (perioperative intravenous/prolonged oral antibiotics) could reduce the  
11  
12 risk of postoperative UTI after UI surgery in a short- and long term perspective. Furthermore, it  
13  
14 would be interesting to assess the use of similar antibiotics in the background population of women  
15  
16 to examine whether there is an increased antibiotic burden associated with surgery for UI.  
17  
18

19  
20 In conclusion, we found that one in four women undergoing surgery for UI was treated for UTI  
21  
22 before surgery, and half of these women continued the tendency of UTI after surgery. In women not  
23  
24 using antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI  
25  
26 after surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of  
27  
28 these antibiotics before surgery.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 **Acknowledgement** None  
5

6 **Funding** This study was funded by 1) Nordic Urogynaecology Association (NUGA) Research  
7  
8 Grant 2) A. P. Møller and Chastine Mc-Kinney Møller Foundation for General Purposes 3) Center  
9  
10 for Clinical Epidemiology, Odense University Hospital, and 4) Region of Southern Denmark  
11  
12

13  
14 **Financial disclaimer/Conflicts of interest** None  
15

16  
17  
18 **Contributors** All authors have drafted the article, revised it critically for important intellectual  
19  
20 content, and approved the finale version to be published. All authors are responsible for the study  
21  
22 concept and design, and participated in the interpretation of data. RG is the guarantor and has full  
23  
24 access to all of the data in the study.  
25  
26

27  
28  
29 **Competing interests** "All authors have completed the ICMJE uniform disclosure form at  
30  
31 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
32  
33 work; no financial relationships with any organisations that might have an interest in the submitted  
34  
35 work in the previous three years.  
36  
37

38  
39  
40 **Ethical approval** The study was approved by the Danish Data Protection Agency (no. 2009-41-  
41  
42 3564). According to Danish law, ethical review board approval or patient consent are not required  
43  
44 for register-based studies.  
45  
46

47  
48  
49 **Copyright** The Corresponding Author has the right to grant on behalf of all authors and does  
50  
51 grant on behalf of all authors, [a worldwide licence](#) to the Publishers and its licensees in perpetuity,  
52  
53 in all forms, formats and media (whether known now or created in the future), to i) publish,  
54  
55 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other  
56  
57  
58  
59  
60



1  
2  
3  
4 languages, create adaptations, reprints, include within collections and create summaries, extracts  
5  
6 and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the  
7  
8 Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic  
9  
10 links from the Contribution to third party material where-ever it may be located; and, vi) licence  
11  
12 any third party to do any or all of the above.  
13  
14

15  
16  
17 **Data sharing** According to the Danish Data Protection Agency, we are not allowed to share our  
18  
19 data from the Danish National Patient Registry. This would require a special approval from both the  
20  
21 Danish Data Protection Agency and the Statens Serum Institut who provides the data from the  
22  
23 Danish National Patient Registry.  
24  
25  
26  
27  
28

### 29 **Article Summary:**

30  
31 **Article focus:** Urinary incontinence is a prevalent disorder among women, and surgery is one of  
32  
33 the major options for treatment. This study focus on the use of antibiotics for urinary tract infection  
34  
35 both before and after surgical treatment of urinary incontinence, and among women using  
36  
37 antibiotics for UTI before surgery to estimate the risk of postoperative use in a short and long term  
38  
39 perspective.  
40  
41  
42

### 43 **Key messages:**

44  
45 One in four woman undergoing surgery for UI was treated for urinary tract infection (UTI) before  
46  
47 surgery, and half of these women continued the tendency of UTIs after surgery. In women not using  
48  
49 antibiotics for UTI before surgery only a minor proportion initiated use of antibiotics for UTI after  
50  
51 surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of these  
52  
53 antibiotics before surgery.  
54  
55  
56  
57  
58  
59  
60

**Strengths and limitations of this study:**

A population-based study.

2,151 included women.

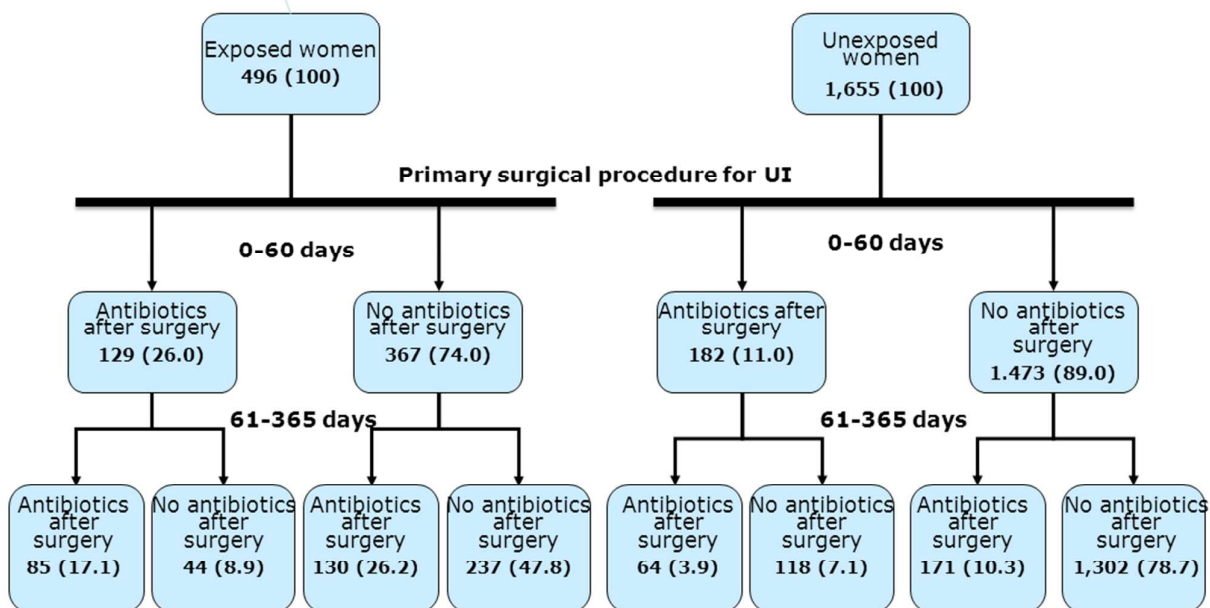
High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on symptomatology, catheter usage, preoperative antibiotics or urine culture.

**Figure 1** Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery. Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.



**Table 1** Baseline characteristics of all included women (N=2,151) having a primary surgical procedure for UI in Denmark, 1996-2010.

	Exposed <sup>a</sup> n=496	Unexposed <sup>b</sup> n=1,655
Mean age (±SD), years (At time of first UI surgery)	60.2 (±13.2)	54.2 (±12.4)
Age groups n (%)		
18-39	30 (6.1)	182 (11.0)
40-59	196 (39.5)	911 (55.1)
60-	270 (54.4)	562 (33.9)
Procedures n (%)		
rpMUS	140 (28.2)	535 (32.3)
toMUS	222 (44.8)	750 (45.3)
Bulking	110 (22.2)	250 (15.1)
Others	24 (4.8)	120 (7.3)
Concomitant prolapse surgery n (%)	12 (2.4)	66 (4.0)
Antibiotics before surgery n (%) <sup>*</sup>		
Sulfamethizol - J01EB02	299 (60.3)	-
Pivmecillinam - J01CA08	288 (58.1)	-
Nitrofurantoin - J01XE01	65 (13.1)	-
Trimethoprim - J01EA01	45 (9.1)	-
Mecillinam - J01CA11	0 (0)	-
Oestrogen users n (%) <sup>**</sup>		
No	211 (42.5)	997 (60.2)
Yes	285 (57.5)	658 (39.8)
Comorbidity (CCI) n (%)		
0	298 (60.1)	1,214 (73.4)
1-2	139 (28.0)	381 (23.0)
3+	59 (11.9)	60 (3.6)
Educational level n (%) <sup>***</sup>		
Basic	229 (47.4)	688 (42.3)
Secondary	170 (35.2)	600 (36.8)
Higher	84 (17.4)	340 (20.9)
Annual income n (%)		
Low (1 <sup>st</sup> quartile)	152 ( <del>25-030.7</del> )	385 (23.3)
Middle (2 <sup>nd</sup> -3 <sup>rd</sup> quartile)	<del>1,077</del> 252 ( <del>50-050.8</del> )	825 (49.9)
High (4 <sup>th</sup> quartile)	<del>537</del> 92 ( <del>25-018.5</del> )	445 (26.9)
Year of surgery n (%)		
1996-2006	106 (21.4)	353 (21.3)
2007-2008	<del>791</del> 186 (37.5)	605 (36.6)
2009-2010	<del>901</del> 204 (41.1)	697 (42.1)

<sup>a</sup>Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery.

<sup>b</sup>Unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.

<sup>\*</sup>Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.

<sup>\*\*</sup>Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

<sup>\*\*\*</sup>Unknown highest attained educational level: 40 women

Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 2** Risk factors of postoperative use of antibiotics. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii), long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,473	182	Reference	1,420	235	reference
Yes	367	129	2.6 (2.0-3.5)	281	215	4.5 (3.5-5.7)
Age group						
18-39	185	27	0.9 (0.5-1.5)	163	49	1.5 (0.9-2.3)
40-59	981	126	0.6 (0.5-0.9)	931	176	0.7 (0.5-0.9)
60+	674	158	Reference	607	225	reference
Procedure						
rpMUS	568	107	1.7 (1.1-2.7)	529	146	1.3 (0.9-1.9)
toMUS	849	123	Reference	782	190	reference
Bulking	315	45	1.4 (0.9-2.0)	278	82	1.1 (0.8-1.5)
Others	108	36	3.1 (1.6-5.9)	112	32	1.5 (0.8-2.8)
Preoperative use of oestrogen*						
No	1,059	149	Reference	992	216	reference
Yes	781	162	1.2 (0.9-1.6)	709	234	1.2 (0.9-1.5)
Comorbidity (CCI)						
0	1,328	184	Reference	1,241	271	reference
1-2	425	95	1.5 (1.1-2.0)	384	136	1.4 (1.1-1.8)
3+	87	32	3.1 (1.6-5.9)	76	43	1.5 (1.0-2.4)
Educational level**						
Basic	775	142	Reference	702	215	reference
Secondary	665	105	1.1 (0.8-1.5)	623	147	1.0 (0.7-1.1)
Higher	362	62	1.3 (0.9-2.0)	342	82	0.9 (0.6-1.3)
Annual income						
Low	434	103	Reference	404	133	reference
Middle	930	147	0.9 (0.6-1.2)	847	230	1.0 (0.8-1.3)
High	476	61	0.9 (0.6-1.4)	450	87	0.9 (0.6-1.3)
Year of surgery						
1996-2006	363	96	1.4 (0.9-2.2)	352	107	0.9 (0.7-1.1)
2007-2008	692	99	Reference	628	163	reference
2009-2010	785	116	1.0 (0.8-1.4)	721	180	1.0 (0.8-1.4)

\*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.

\*\*Unknown highest attained educational level: 40 women

Abbreviations: Post op=postoperative, OR = odds ratio, CI = confidence interval , rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

**Table 3** Stratified analyses according to use of oestrogen before surgery for UI to examine the association between preoperative use of antibiotics for urinary tract infection and postoperative use.

Preop.	Preop.	Crude OR (95% CI)	Adj. OR* (95% CI)	Crude OR (95% CI)	Adj. OR* (95% CI)
oestrogen n	antibiotics n	Short term	Short term	Long term	Long term
Yes 943	Yes 285	3.5 (2.5-5.0)	3.3 (2.3-4.8)	5.2 (3.8-7.2)	5.2 (3.7-7.3)
	No 658				
No 1.208	Yes 211	2.0 (1.3-2.9)	2.0 (1.3-3.0)	3.8 (2.7-5.2)	3.7 (2.6-5.3)
	No 997				

\*Adjusted for age, procedure type, comorbidity, educational level, annual income, and calendar year of surgery.  
Abbreviations: Preop. = preoperative, Adj. = adjusted, OR = odds ratio, CI = confidence interval

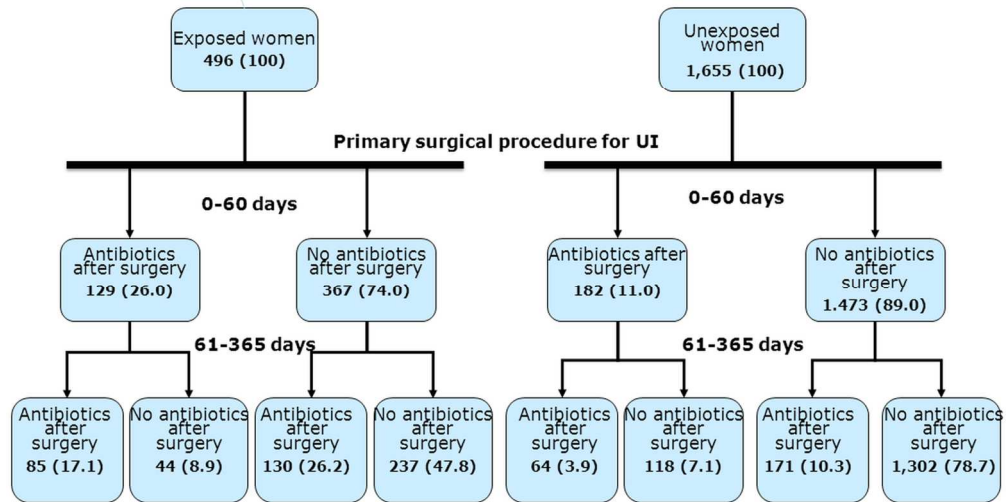
## References

1. Foxman B. Recurring urinary tract infection: incidence and risk factors. *Am J Public Health* 1990;80:331–3.
2. Athanasiou S, Anstaklis A, Betsi GI, et al. Clinical and urodynamic parameters associated with history of urinary tract infections in women. *Acta Obstet Gynecol Scand* 2007;86:1130–5.
3. Hu KK, Boyko EJ, Scholes D, et al. Risk factors for urinary tract infections in postmenopausal women. *Archives of internal medicine* 2004;164:989–93.
4. Raz R, Gennesin Y, Wasser J, et al. Recurrent urinary tract infections in postmenopausal women. *Clin Infec Diseases* 2000;30:152–6.
5. Bodhare TN, Valsangkar S, Bele SD. An epidemiological study of urinary incontinence and its impact on quality of life among women aged 35 years and above in a rural area. *Indian IJU* 2010;26:353–8.
6. Fok CS, McKinley K, Mueller ER, et al. Day of surgery urine cultures identify urogynecologic patients at increased risk for postoperative urinary tract infection. *J Urol* 2013;189:1721–4.
7. Sutkin G, Alperin M, Meyn L, et al. Symptomatic urinary tract infections after surgery for prolapse and/or incontinence. *Int Urogynecol J* 2010;21:955–61.
8. Nygaard I, Brubaker L, Chai TC, et al. Risk factors for urinary tract infection following incontinence surgery. *Int Urogynecol J* 2011;22:1255–65.
9. Ingber MS, Vasavada SP, Firoozi F, Goldman HB. Incidence of perioperative urinary tract infection after single-dose antibiotic therapy for midurethral slings. *Urol* 2010;76:830–4.
10. Jackson D, Higgins E, Bracken J, Al E. Antibiotic Prophylaxis for Urinary Tract Infection After Midurethral Sling: A Randomized Controlled Trial. *Fem Pelv Med & Reconstr Surg* 2013;19:137–41.
11. Anger J, Litwin M, Wang Q, Al E. Complications of sling surgery among female Medicare beneficiaries. *Obstet Gynecol* 2007;109:707–14.
12. Stanford EJ, Paraiso MFR. A comprehensive review of suburethral sling procedure complications. *J Minimally Inv Gynecology* 1999;15:132–45.
13. LaSala C a, Schimpf MO, Udoh E, et al. Outcome of tension-free vaginal tape procedure when complicated by intraoperative cystotomy. *Am J Obstet Gynecol* 2006;195:1857–61.
14. Pugsley H, Barbrook C, Mayne CJ, Tincello DG. Morbidity of incontinence surgery in women over 70 years old: a retrospective cohort study. *BJOG* 2005;112:786–90.

15. Ward K, Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002;325:67.
16. Tamussino K, Hanzal E, Kolle D, Al E. Tension-free vaginal tape operation: results of the Austrian registry. *Obstet Gynecol* 2001;98:732–6.
17. Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association ( IUGA )/ International Continence Society ( ICS ) Joint Terminology and Classification of the Complications Related Directly to the Insertion of Prostheses ( Meshes , Implants , Tapes ) and Grafts in Female P. *Int Urogynecol J* 2011;22:3-15.
18. Lyng E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–5.
20. Andersen T, Madsen M, Jørgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:262–8.
21. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-8). Geneva, Switzerland; 1967.
22. World Health Organization. International Classification of Diseases - 10th revision (ICD-10) [Internet]. 2013. Available from: <http://www.who.int/classifications/ics/en/>
23. Nordic Medico-Statistical Committee. Classification of Surgical Procedures, version 1.15. 2010 no. 93.
24. Gaist D, Sørensen H, Hallas J. The Danish Prescription Registers. *Dan Med Bull*. 1997;44:445–8.
25. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011;39:95–8.
26. Bjerrum L, Grindsted P. How to treat uncomplicated cystitis? *Ugeskr Laeger*. 2000;162:197–8 [Danish].
27. Bjerrum L, Dessau R, Hallas J. Treatment failures after antibiotic therapy of uncomplicated urinary tract infections. A prescription study. *Scand J Primary Health Care*. 2002;20:97–101.
28. Dalton SO, Steding-Jessen M, Engholm G, et al. Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 2008;44:1989–95.
29. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–83.



- 1  
2  
3  
4 30. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies  
5 using administrative databases. *Int J Epidemiol* 2000;29:891–8.  
6  
7 31. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10  
8 diagnostic coding used to assess Charlson comorbidity index conditions in the population-  
9 based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.  
10  
11 32. Thomsen R, Riis A, Christensen S, et al. Diabetes and 30-Day Mortality From A Danish  
12 population-based cohort study. *Diabetes Care*. 2006;29:805–10.  
13  
14 33. Svenningsen R, Borstad E, Spydslaug AE, et al. Occult incontinence as predictor for  
15 postoperative stress urinary incontinence following pelvic organ prolapse surgery. *Int*  
16 *Urogynecol J* 2012;23:843–9.  
17  
18 34. Andersen T, Madsen M, Loft A. Validity of surgical information from the Danish National  
19 Patient Registry with special attention to the analysis of regional variations in hysterectomy  
20 rates. *Ugeskr Laeger* 1987;149:2420–2 [Danish].  
21  
22 35. Mosbech J, Jørgensen J, Madsen M, et al. The national patient registry. Evaluation of data  
23 quality. *Ugeskr Laeger* 1995;157:3741–5 [Danish].  
24  
25 36. Ottesen M. Validity of the registration and reporting of vaginal prolapse surgery. *Ugeskr*  
26 *Laeger* 2009;171:404–8 [Danish].  
27  
28 37. Guldberg R, Brostrøm S, Hansen JK, et al. The Danish Urogynaecological Database:  
29 establishment, completeness and validity. *Int Urogynecol J* 2013;24:983–90.  
30  
31 38. Wald H, Ma A, Bratzler D, Al E. Indwelling Urinary Catheter Use in the Postoperative  
32 Period. *Arch Sur*. 2008;143:551–7.  
33  
34 39. Platt R, Polk B, Murdock B, Al. E. Risk factors for nosocomial urinary tract infection. *Am J*  
35 *of Epidemiol*. 1986;124:977–85.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI.

view only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1 – Title page
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	3+6-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+6-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10+11
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11 + Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 + Table 2
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	13
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).