

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence - a cohort study
AUTHORS	Guldberg, Rikke; Kesmodel, Ulrik; Brostrøm, Søren; Kærlev, Linda; Hansen, Jesper; Hallas, Jesper; Nørgård, Bente

VERSION 1 - REVIEW

REVIEWER	Adrian Wagg University of Alberta Edmonton Canada
REVIEW RETURNED	11-Nov-2013

GENERAL COMMENTS	<p>Reviewer's report: Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence – a cohort study</p> <p>The aim of this study was to describe the use of antibiotics for urinary tract infection before and after surgery for urinary incontinence and for those with use of antibiotics before surgery, to estimate the risk of treatment for a post-operative urinary tract infection relative to those with no use.</p> <p>Introduction: The authors might include some discussion about the difficulties of case ascertainment of “true UTI” and how the quoted studies may have been biased because of the varying definition of UTI. Additionally, to what extent do the authors feel that the association between UI and UTI is confounded because of active surveillance and overtreatment of what might be considered bacteriuria in a person with UI, where there is no causal link. The authors do not really make the case for the importance of the research question – why is it important to know this risk in this particular fashion?</p> <p>Materials and methods: The obvious methodological problem here is the lack of a control group – one cannot know whether the post-operative group have any different UTI incidence to a group of age matched women who have not had an operation. The method is well described and this cohort has been used for a study of anti-incontinence drugs around surgery for UI.</p> <p>The proportion of utis missed as they were treated with antibiotics not under surveillance appears inestimable. Antibiotics such as trimethoprim are also occasionally used for chest infections, I'm sue the authors have acknowledged this limitation further on in the paper.</p> <p>Please could the authors suggest why their surveillance began 1</p>
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	<p>year prior to the index date – this seems inordinately long for what is essentially a short episode of treatment?</p> <p>In terms of covariates, would not recurrent use of antibiotics prior to the procedure also increase the likelihood of post-operative use?</p> <p>What was the reason for including systemic oestrogen prescriptions in the model – what evidence is there that these have an effect on UTI incidence?</p> <p>Given that antibiotics are cheap, what evidence is there that there is that there is variation in usage with socioeconomic status?</p> <p>What evidence is there to suggest that UTI incidence might vary between transobturator versus retropubic MUS?</p> <p>Results:</p> <p>Annoyingly, I can't seem to view figure 1 in the pdf, but have the legend</p> <p>Was there a differential risk in being a remote pre-operative user versus a recent pre-operative user of antibiotics?</p> <p>Otherwise the results seem well presented with an appropriate mix of tables and text It might be interesting to examine whether there is an increased antibiotic burden associated with operations for incontinence. I don't see this analysis</p> <p>Discussion</p> <p>The limitations of the study are well outlined. The difficulty of case ascertainment needs discussion – does receipt of antibiotics equal UTI? What effect do the authors think that the rate of “success” of the operation might have in terms of continuing prescription of antibiotics in pre-operative users?</p> <p>There's a typo on page 14, line 54</p> <p>The discussion on probability of active prescriptions is useful, particularly that of prescriber characteristics</p>
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REVIEWER	Mr Ghulam Nabi University of Dundee
REVIEW RETURNED	28-Nov-2013

GENERAL COMMENTS	<p>The manuscript describe antibiotic prescription trend in a large cohort of post-incontinence surgery patients. The paper has some methodological flaws which need to addressed:</p> <ol style="list-style-type: none"> 1. It is a retrospective data and hence cannot be free of know biases associated with any such designs 2. Indications for antibiotic prescription are not stated and reader will remain unaware as whether prescription in the first instance was generated by non-specific symptoms or culture proven UTI. 3. We know that symptoms especially post surgical procedure in urinary incontinence could be unreliable in predicting UTI and hence empirical use of antibiotics could be a major issue here. 4. It would be useful to know what authors means by pre-operative use o antibiotics. Do they mean a single prophylactic dose or use of antibiotics for a longer period prior to surgery? The latter could be a reason for antibiotic resistance and hence repeat treatment.
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	<p>5. "Antibiotic use" is quite a broad term and it is extremely useful to comment which antibiotic was most commonly used prior to surgery and then repeated.</p> <p>6. What is the general antibiotics resistance in the country authors belong to></p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Introduction:

The authors might include some discussion about the difficulties of case ascertainment of “true UTI” and how the quoted studies may have been biased because of the varying definition of UTI. This is an important comment as there are actually varying definitions of UTI leading to differences in case ascertainment across the studies. This has been raised in the introduction section in the manuscript, page 5: UTI after surgery might occur among 6-38% of the women – depending on diagnostic methods and criteria (references 8,10-16).

In the first version of this manuscript the percentage was written as one number (34%) – this has been corrected to an interval based on the percentages for UTI postoperatively reported in the references.

To what extent do the authors feel that the association between UI and UTI is confounded because of active surveillance and overtreatment of what might be considered bacteriuria in a person with UI, where there is no causal link.

In Denmark, dipstick urine test is a part of the preoperative examination, and surgeons might feel encouraged to treat the women with antibiotics prior to surgery based on dipstick urine test without symptoms or urine culture in an attempt to try to minimize the risk of postoperative UTI. This has been added to the discussion section, page 14.

The authors do not really make the case for the importance of the research question – why is it important to know this risk in this particular fashion?

Thank you. A sentence to clarify why the research question is important has been added to the introduction, page 5:

“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:

The obvious methodological problem here is the lack of a control group – one cannot know whether the post-operative group have any different UTI incidence to a group of age matched women who have not had an operation.

Our study-population was designed to include only women having an operation – and thus we did not have a group of women without an operation. As written on page 9 the exposed cohort constituted women undergoing primary surgical procedure for UI and having redeemed one or more prescriptions on antibiotics within 365 days preceding the date of surgery (index date), and the unexposed cohort constituted women undergoing a primary surgical procedure for UI without having redeemed similar prescriptions within the same time frame.

The proportion of utis missed as they were treated with antibiotics not under surveillance appears inestimable. Antibiotics such as trimethoprim are also occasionally used for chest infections, I’m sue the authors have acknowledged this limitation further on in the paper.

The antibiotics not under surveillance have a broader spectrum of infections disorders than UTI as indications. By leaving these antibiotics out of our study may lead to an underestimation of the risk of UTI which was mentioned in the discussion on page 14. In Denmark, Trimethoprim is exclusively/predominantly used for UTI as stated on page 7.

Please could the authors suggest why their surveillance began 1 year prior to the index date – this

seems inordinately long for what is essentially a short episode of treatment?

Treatment of UTI is a short episode. The reason for a period of 365 days prior to surgery was to have the information on numbers of prescriptions prior to surgery as a measure of possible recurrent UTIs.

The majority of the women redeemed less than 3 prescriptions (as mentioned on page 11).

Only 8% redeemed more than five or more prescriptions. This has been added to the result section, page 11.

In terms of covariates, would not recurrent use of antibiotics prior to the procedure also increase the likelihood of post-operative use?

The majority (376/496=75.8%) redeemed one or two prescriptions preoperatively. As the preoperatively redeemed prescriptions were only in the exposed cohort, this was not possible to include as a covariate in the regression model.

What was the reason for including systemic oestrogen prescriptions in the model – what evidence is there that these have an effect on UTI incidence?

We found a difference in preoperative oestrogen users among the exposed cohort and the unexposed cohort as shown in Table 1. Theoretically, oestrogen could be protective against UTI postoperatively. Furthermore, oestrogen is in the literature suggested to prevent repeat urinary tract infections in postmenopausal women.

The clinical practice in Denmark is that nearly all menopausal women are treated with local oestrogen prior to surgery. The majority of women in our study population were peri- or postmenopausal. Therefore, we decided to include oestrogen in the model

Given that antibiotics are cheap, what evidence is there that there is variation in usage with socioeconomic status?

In the literature there are to our knowledge no evidence of socioeconomic status could confound the association in our study.

To address possible criticism of not including socioeconomic status in a pharmacoepidemiological study, we decided to obtain this information.

Even though both educational level and personal income in this study seemed not to be important according to the logistic regression model with little influence on our estimates, we have decided to maintain these in the model as these factors usually are well-known and important confounders in many pharmacoepidemiological studies.

And furthermore, we believe that this actually contribute with new information, since in this context the socioeconomic status is of less importance to the association under study.

What evidence is there to suggest that UTI incidence might vary between transobturator versus retropubic MUS?

In retropubic MUS a preoperative cystoscopy is standard due to the risk of bladder perforation, and thus introducing the risk of UTI. This has not been standard at the transobturator MUS because of the different route, and thus this type of procedure could have a lower risk of UTI as a postoperative complication. In this study we found that rpMUS has a higher risk of UTI within 60 days after surgery: rpMUS OR 1.7 for postoperative short term antibiotic use, Table 2.

Results:

Annoyingly, I can't seem to view figure 1 in the pdf, but have the legend. Was there a differential risk in being a remote pre-operative user versus a recent pre-operative user of antibiotics?

Figure 1 has now been added within the text, page 20 and not uploaded as a separate file as before.

Among the exposed women, 26.0% continued with antibiotics within 0-60 days after surgery, and 43.3% within 61-365 days after surgery.

Among the unexposed women, 11.0% continued with antibiotics within 0-60 days after surgery, and 14.2% within 61-365 days after surgery.

It might be interesting to examine whether there is an increased antibiotic burden associated with operations for incontinence. I don't see this analysis

This is an important and relevant comment.

In this study we have not included women without surgery and this would be interesting and has been proposed in the discussion section page 16 as suggestion for future studies.

Within our two cohorts of women, we can conclude that there was an increased antibiotic burden associated with operations in the women with preoperatively prescriptions of antibiotics for UTI compared to women without preoperatively similar prescriptions.

Discussion

The difficulty of case ascertainment needs discussion – does receipt of antibiotics equal UTI?

A redeemed prescription of antibiotics for UTI does not necessarily equal UTI, and urine culture is not always performed prior to a prescription. Thus, empiric therapy is possible.

This has been added to the discussion section, page 14.

What effect do the authors think that the rate of “success” of the operation might have in terms of continuing prescription of antibiotics in pre-operative users?

“Success ” of an operation depends of multiple factors such as subjective cure from the patients point of view, objective cure from the doctors point of view, complications (both pre- and postoperatively), re-operation, and repeated surgery. Furthermore a time dimension is also important.

This study does not account for all the above, and contributes only with a small bite of this complex question of success. In this study nearly half of the preoperative users continued being users postoperatively and thus the other half of the preoperatively users were no longer users after surgery.

There's a typo on page 14, line 54

Typos have been corrected on page 11 and 14.

2. Reviewer

Indications for antibiotic prescription are not stated and reader will remain unaware as whether prescription in the first instance was generated by non-specific symptoms or culture proven UTI. You are right – indications are not included in this register-based study and thus lacking. This kind of information is not available in the registers used in this study and therefore mentioned as a limitation in the discussion section in the manuscript, page 14.

We know that symptoms especially post surgical procedure in urinary incontinence could be unreliable in predicting UTI and hence empirical use of antibiotics could be a major issue here. Our study is based on surgical procedures and redeemed prescriptions. We have no information on symptoms or urine culture which is a limitation as stated in the discussion section in the manuscript page 14.

Since urine culture is not always performed prior to prescriptions of antibiotics for UTI, empiric therapy is possible. This has been added to the discussion section, page 14.

It would be useful to know what authors means by pre-operative use of antibiotics. Do they mean a single prophylactic dose or use of antibiotics for a longer period prior to surgery? The latter could be a reason for antibiotic resistance and hence repeat treatment.

Pre-operative use of antibiotics in this manuscript is an oral treatment usually lasting 3-5 days. This has been emphasized in the manuscript in the material and methods section, page 7.

"Antibiotic use" is quite a broad term and it is extremely useful to comment which antibiotic was most commonly used prior to surgery and then repeated.

The two most commonly used antibiotics both pre- and postoperatively have been added to the Result section, page 11.

What is the general antibiotics resistance in the country authors belong to

According to the Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans, the resistance for non-E coli infections, has increased during the last years. However, E coli is the most frequent cause of UTIs both in community and hospital-acquired UTIs. This has been added to the discussion section, page 15.