PREVENTION OF CATHETER-ASSOCIATED URINARY TRACT INFECTION FOLLOWING GYNAECOLOGIC SURGERY: A SYSTEMATIC REVIEW

*Christine M. Chu, Lily A. Arya

Division of Urogynecology, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, USA

*Correspondence to christinem.chu@uphs.upenn.edu

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ABSTRACT

Catheter-associated urinary tract infection (CAUTI) is the most common postoperative infection associated with gynaecologic procedures, and results in increased risks to patients and costs for hospitals. Currently, there is great variation in chemoprophylaxis used for prevention of postoperative CAUTI. The objective of this paper was to systematically review the efficacy of chemoprophylaxis for the prevention of CAUTI during short-term catheterisation following gynaecologic surgery. Evidence acquisition was undertaken by performing a systematic review of PubMed/Medline, Scopus, and the Cochrane Library in November 2013 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Quality assessment was performed using the Jadad and Newcastle-Ontario Scales. Nine studies met criteria for inclusion. Included publications used either antibiotics or methenamine hippurate for chemoprophylaxis. Chemoprophylaxis during catheterisation resulted in a statistically significant decrease in significant bacteriuria as compared to control groups in the majority of the studies. Symptomatic bacteriuria was also significantly decreased. A recommendation of a specific regimen for chemoprophylaxis cannot be made due to heterogeneity in study quality, dose, and duration of chemoprophylaxis, timing of urine culture, and study endpoints. Evidence examining cost-effectiveness and antibiotic resistance was limited. We reviewed the use of either antibiotics or methenamine hippurate for the prevention of CAUTI after gynaecologic surgery. Evidence suggests that chemoprophylaxis results in a decreased rate of bacteriuria and UTIs postoperatively. Further studies are required to determine the optimum regimen. Chemoprophylaxis is useful for the prevention of CAUTI during short-term catheterisation after gynaecologic surgery. Further research to determine the most effective type and dose of chemoprophylaxis, as well as cost-effectiveness and the potential development of antibiotic resistance, is needed.

Keywords: Antibiotic prophylaxis, catheter-associated urinary tract infection, gynaecology, methenamine hippurate, prevention, short-term catheterisation, surgical patients, urinary catheter, urinary tract infection, urogynaecology.

INTRODUCTION

Catheter-associated urinary tract infection (CAUTI) after catheterisation is an increasingly important issue in gynaecology as it is one of the most common infections that occur after gynaecologic surgery. Women undergoing urogynaecologic procedures, such as surgery for pelvic organ prolapse and urinary incontinence, are particularly susceptible to post-surgical CAUTI because of urinary tract instrumentation and post-menopausal status, as well as the high rates of transient postoperative urinary retention requiring short-term indwelling catheter use. Rates of urinary tract infection (UTI) within 6 weeks of urogynaecologic surgery were estimated to be 16.8% in patients who failed their void trials, and up to 33.6% within 3 months of mid-urethral sling placement.
Significant bacteriuria or positive urine culture is defined as ≥10^5 colony-forming units per ml of urine with no more than two species of microorganisms. Symptomatic UTI is defined as at least one or more signs or symptoms (fever >38°C, suprapubic tenderness, costovertebral angle tenderness, dysuria, urgency, frequency), positive urine dipstick for leukocyte esterase and/or nitrite, or pyuria or microorganisms on microscopy, and a positive urine culture. CAUTI is defined by the Center for Disease Control as asymptomatic UTI associated with indwelling catheters in place for at least 2 days, or removed within 2 days of diagnosis of symptomatic UTI. In published studies, there is considerable variation in the combination of symptoms and signs used to define symptomatic UTI; several studies define significant bacteriuria at lower colony counts, and CAUTI as any UTI within 6 weeks of catheter removal.

Prevention of postoperative CAUTI is important for both patients and healthcare systems. UTIs can lead to complications such as pyelonephritis and bacteraemia, which require treatment with antibiotics and increased hospitalisation. CAUTI increases the economic burden on both patients and physicians, as UTI results in 8.3 million office visits a year, and each CAUTI costs approximately $600 per episode. CAUTI has become costly for hospitals as well; in the United States, the Centers for Medicare and Medicaid Services (CMS) have not been compensating hospitals for UTIs related to catheterisation since 1st October, 2008.

Chemoprevention with antibiotics or antiseptics such as methenamine can potentially decrease the chance of UTI after postoperative catheterisation. Both the American Urologic Association (AUA) and the American College of Obstetrics and Gynecology (ACOG) recommend considering prophylactic antibiotics for catheter removal. AUA guidelines suggest that antimicrobial use may be warranted “at the time of catheter removal following urinary tract surgery”, especially in patients with risk factors such as advanced age, anatomic anomalies, and immunodeficiencies; however, treatment may also be deferred and based on urine culture at catheter removal. According to ACOG guidelines: “Daily antibiotic prophylaxis should be considered in women discharged with an indwelling urinary catheter after urogynaecologic surgery.” The above recommendations for chemoprophylaxis for short-term postoperative catheter use are mostly based on non-gynaecologic populations and there are no specific recommendations on the choice and dose of the agent. The aim of this study is to systematically review the efficacy of different types of chemoprophylaxis used to prevent CAUTI after short-term catheterisation following gynaecologic surgery.

**MATERIALS AND METHODS**

Literature searches were performed using PubMed/Medline, Scopus, and Cochrane Central Register of Controlled Trials for studies published from 1947 to November 2013. With the assistance of a medical librarian, we searched for studies with the following keywords and MeSH terms in different search combinations: “UTI”, “catheter-associated UTI”, “urinary catheter”, “removal”, “device removal”, “prevention”, “prophylaxis”, “gynaecology”, “urogynaecology”, “gynaecologic surgery”, “antibiotic”, “antibiotic prophylaxis”, “anti-infective agents”, “anti-infective agents, urinary”, “anti-septic”, “methenamine”, “hippurates”, and “Hiprex”. We included both English and non-English language studies. Titles and abstracts of eligible studies were screened, and potentially-eligible papers were obtained for full review. These papers were reviewed before inclusion into the review.

Articles were assessed for relevance, and those unrelated to CAUTI and chemoprophylaxis - with either antibiotics or methenamine hippurate - were excluded. Titles and abstracts were excluded if: 1) the study was not a randomised controlled or prospective cohort design; 2) the patients included had not undergone either gynaecologic or urogynaecologic surgery; 3) antibiotics were given at or until the time of catheter removal; and 4) measurement of the outcome of bacteriuria was not performed. Short-term catheterisation was defined as ≤14 days. The primary endpoint for this review was symptomatic UTI, as defined by one sign or symptom of UTI and significant bacteriuria. The secondary outcome was significant bacteriuria as defined in the specific study.

Included articles underwent data abstraction. Information abstracted included: 1) year of publication; 2) study design; 3) number of patients who received chemoprophylaxis; 4) number of patients who did not receive chemoprophylaxis or received placebo; 5) number of days patients underwent indwelling urinary catheterisation; 6) type of chemoprophylaxis; 7) duration and
dose of chemoprophylaxis; 8) duration of post-catheterisation follow-up; 9) proportion of patients who had significant bacteriuria; 10) proportion of patients who had symptomatic bacteriuria, if measured.

Assessment of methodological quality was performed using the Jadad scale for randomised controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. The Jadad scale evaluates three aspects of RCTs: randomisation, blinding, and patient drop-out/withdrawals. All areas except patient drop-out are assigned two points, for a total score of zero (low quality) to five (high quality), with the potential to eliminate points based on the quality of description of the randomisation and blinding processes. It has been found to have high reliability and validity compared to other scales of assessment. The NOS is a commonly used scale for quality evaluation of cohort studies that has been recommended by The Cochrane Collaboration. The NOS contains three parts: selection, comparability, and outcome - with a total of eight questions. Each item can be awarded up to one star, except for comparability, which may earn two; scores, therefore, range from zero to nine.

RESULTS

The study selection process is described in Figure 1. The initial search resulted in 4,708 publications, which, after evaluation of titles and abstracts, led to 60 articles being considered for full evaluation. After the removal of duplicates, 34 articles were considered. However, 7 articles were excluded for study design, 14 studies were excluded for population, and 4 articles were excluded for intervention not consistent with the objectives of this review.

Out of the nine studies that met inclusion criteria, five studies investigated the use of methenamine while three studies examined the use of antibiotics as prophylaxis for CAUTIs. One study included a comparison of an antibiotic and methenamine. Seven of these studies were RCTs while two studies (one on methenamine and one on prulifloxacin) were prospective observational cohort studies. Of the RCTs included in the review, three provided description of their randomisation process. Three studies were conducted as a double-blind, randomised, placebo-controlled study.

Table 1 shows the rating of the RCTs included in this review according to the Jadad Scale, while Table 2 shows the quality of the prospective cohort studies rated according to the NOS. There was considerable heterogeneity between studies in the chemoprophylaxis regimens, duration of use, and outcomes measured, which prevented us from performing a meta-analysis.

Table 3 shows the study design and outcomes of the nine studies included in this review. Two out of six studies that investigated methenamine were conducted in patients undergoing urogynaecologic procedures only; similarly, three out of four studies that investigated the use of antibiotics were performed in patients undergoing urogynaecologic procedures. All other studies involved a mix of patients undergoing a variety of general gynaecologic and urogynaecologic procedures. Out of all nine studies, eight studies used indwelling catheters; Rogers et al. however, used suprapubic catheters in the postoperative period.

Four studies investigated the use of prophylactic antibiotics for the prevention of CAUTIs. Antibiotics used in the studies were quite heterogeneous, and included three different classes of antibiotics (nitrofurantoin, fluoroquinolones, and sulfa antibiotics). Rogers et al. studied the use of nitrofurantoin for prophylaxis, while Ghezzi et al. examined the use of sulfamethizole (a bacteriostatic antibiotic) solely, with a total daily dose of 1,000 mg, while Baertschi et al. used trimethoprim-sulfamethoxazole in a daily dose of 320 mg trimethoprim and 1,600 mg sulfamethoxazole.

There was a lack of consistency in antibiotic regimens as well. Ghezzi et al. was the only study to use a one-dose regimen prior to catheter removal. All other studies provided daily prophylaxis at least until catheter removal, but two studies started prophylaxis prior to surgery and one study provided an additional 2-6 days prophylaxis after catheter removal.

Six studies investigated the use of prophylactic methenamine hippurate for the prevention of CAUTIs. Regimens again varied, with the total daily dose ranging from 1-4 g (with most studies using 2 g daily), initiated 1-2 days prior
to surgery, and ending anywhere from catheter removal to 3 days post-catheter removal. Thomlinson et al.\textsuperscript{16} added sodium acid phosphate to their methenamine regimen for further urine acidification.

The duration of catheterisation also varied considerably between studies, although duration in all nine studies was similar between treatment and control groups within studies.

Bacteriuria, as measured by urine culture, was reported as an outcome in all studies although there was a considerable difference across studies in the timing of urine collection. Most studies included a pre-surgical specimen (except for Murray et al.\textsuperscript{21}). Several studies examined urine collected at catheter removal\textsuperscript{,2,18-21} and every study examined urine collected in the post-catheter period (ranging from 2-8 days after catheter removal). Additional follow-up urine cultures, at time periods ranging from 1 week to 6-8 weeks after surgery, was performed in three studies\textsuperscript{.2,18-19}

Five of the nine studies did not specify the technique by which urine was collected at each follow-up\textsuperscript{.14-16,19,20}. Remaining studies provided specific descriptions of follow-up by aseptic catheter collection or mid-stream urine collection\textsuperscript{.2,17,18,21}. Most studies defined significant bacteriuria as $>10^5$ cfu/ml, although three studies provided lower limits in their definition of significant bacteriuria for catheter-collected specimens (ranging from $10^3$ to $10^4$ cfu/ml)\textsuperscript{.2,18,20}

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**Figure 1: Selection process for the included studies in this systematic review.**
Five studies examined symptomatic bacteriuria (UTI) as a secondary endpoint, usually defined as a positive urine culture with at least one symptom of UTI. Two of the three studies that investigated treatment with antibiotics reported reduction in the incidence of symptomatic UTI after short-term postoperative indwelling catheter. Baertschi et al. did not report the rate of symptomatic UTI after treatment with trimethoprim-sulfamethoxazole. Significant bacteriuria was decreased at the time of catheter removal following treatment with any antibiotic compared to control. At additional follow-up cultures after surgery, significant bacteriuria decreased on treatment with any antibiotic; however, this difference did not reach significant levels.

The majority of the studies reported that chemoprophylaxis with methenamine resulted in the reduction of both symptomatic bacteriuria and significant bacteriuria. The three studies that examined symptomatic UTI reported a significant decrease in this outcome with the use of methenamine prophylaxis. Four of five studies found a significant decrease in bacteriuria, while one study found no significant difference.

### Table 1: Rating of randomised controlled trials on chemoprophylaxis for catheter-associated urinary tract infection following gynaecologic surgery (Jadad Scale).

<table>
<thead>
<tr>
<th>Study</th>
<th>Random allocation</th>
<th>Blinding</th>
<th>Dropout/Withdrawal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers et al.</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Baertschi et al.</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Murray et al.</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Schiøtz et al.</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Tyerman et al.</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Knoff et al.</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ladehoff et al.</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Jadad Scale: scores range from 0-5, with 5 being high quality.

### Table 2: Rating of prospective cohort studies on chemoprophylaxis for catheter-associated urinary tract infection following gynaecologic surgery (Newcastle-Ottawa Scale).

<table>
<thead>
<tr>
<th>Study</th>
<th>Representation of exposed cohort</th>
<th>Selection of non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at the start of the study</th>
<th>Comparability of cohorts</th>
<th>Assessment of outcome</th>
<th>Was follow-up long enough for outcome to occur</th>
<th>Adequacy of follow-up of cohorts</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghezzi et al.</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>7</td>
</tr>
<tr>
<td>Thomlinson et al.</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>7</td>
</tr>
</tbody>
</table>

Newcastle-Ottawa Scale: scores range from 0-9, with 9 being high quality; 1 star is awarded for each category except for comparability.
In the only study comparing methenamine with an antibiotic agent (sulphamethizole), Murray et al.\textsuperscript{21} found no statistically significant difference between the two agents in the incidence of significant bacteriuria.

Side-effects and adverse events secondary to treatment were reported in six studies. A rash was observed in patients treated with methenamine, as well as trimethoprim-sulfamethoxazole.\textsuperscript{2,20} Gastrointestinal symptoms were common, including diarrhea,\textsuperscript{18} nausea and vomiting,\textsuperscript{2,19,20} and gastro-oesophageal reflux disease.\textsuperscript{4,20}

Ghezzi et al.\textsuperscript{19} also examined the effect of antibiotic use on vaginal microflora through lactobacillary grade on wet mount or culture. In their study, no patients were found to have any significant change in lactobacillary flora 1 week after surgery in either the treatment or placebo group. Tyreman et al.\textsuperscript{17} noted decreased UTI due to opportunistic infections in patients treated with methenamine. Only one study examined bacterial resistance in patients with significant bacteriuria, and reported greater frequency of resistance in the treatment group than the placebo group.\textsuperscript{20}

**DISCUSSION**

The majority of the studies included in this review report a statistically significant benefit from the use of chemoprophylaxis, with either antibiotic or methenamine prophylaxis, for the prevention of CAUTI after gynaecological procedures. Our findings are consistent with a recent meta-analysis that investigated antibiotic prophylaxis at catheter removal in patients who have undergone a wide variety of surgical procedures. Unlike this meta-analysis, our review includes chemoprophylaxis with either antibiotic or methenamine, and focuses on CAUTI following gynaecologic surgery.\textsuperscript{22} In our review, the six studies that examined symptomatic UTI noted a significant decrease in symptomatic UTIs, ranging from 0-19% after antibiotic use and 2-3% after methenamine hippurate, as compared to 0-41% in controls.\textsuperscript{2,14,17-20} Rates of significant bacteriuria were also significantly lower after treatment by antibiotics or methenamine, ranging from 0-46% and 3-35%, respectively, as compared to 4.3-50% in controls.

Though the majority of the studies show that chemoprophylaxis with antibiotics or methenamine is effective in preventing CAUTI, considerable heterogeneity across studies does not allow us to recommend an optimal regimen for chemoprophylaxis. There is a lack of consistency across studies in the dose of chemoprophylactic agent, duration of administration, duration of catheter use, timing and technique of collection of urine specimen, and the primary outcome (bacteriuria versus symptomatic UTI). Additionally, the majority of the studies have a small sample size, and only a few studies\textsuperscript{2,18,19} report a sample size calculation. The quality of the studies on prophylactic antibiotics was poor to good, with the Jadad scale score averaging 3.3 while the NOS score of the cohort trial was 7 out of 9. Likewise, the quality of the studies on methenamine ranged widely, with the average Jadad scale averaging 3, and a NOS score of 7 out of 9. Furthermore, as *Escherichia coli* resistance to trimethoprim-sulfamethoxazole and ciprofloxacin is greater than to nitrofurantoin,\textsuperscript{23} further studies on nitrofurantoin may be more clinically relevant. Only one study in our review examined the use of nitrofurantoin as a prophylactic agent.\textsuperscript{19} There is also considerable heterogeneity across studies in the outcome used to measure the effectiveness of the chemoprophylactic regimen. Although many studies defined bacteriuria as $>10^5$ colony-forming units per ml, several studies had a lower threshold for catheterised specimens ($>10^3$-4). This lower threshold is traditionally used for direct bladder puncture or clean catheterisation, and may not be as useful for indwelling catheters. Irrespective of which definition is used, significant bacteriuria may not be a clinically meaningful endpoint in the prevention of CAUTI. Prior studies suggest that treatment of asymptomatic bacteriuria is not required after minor urologic procedures that do not involve bladder mucosal trauma.\textsuperscript{24} In 40% of patients, significant bacteriuria resolves spontaneously, and only about 11-33% of patients with significant bacteriuria became symptomatic.\textsuperscript{21,19} Therefore, symptomatic bacteriuria (symptomatic UTI) may be a more clinically relevant endpoint. Half of the studies included in the review did not examine this as an endpoint. Future research should also include the rate of symptomatic UTI after chemoprophylaxis as either a primary or secondary outcome.

Adverse effects, costs, and side-effects are important considerations in the use of prophylaxis at the time of catheter removal. This review shows...
that although prophylaxis is not without side-effects, they are generally minor and affect a small number of patients. Though the prescription of chemoprophylaxis would increase costs for hospitals and healthcare systems alike, no studies performed cost-analysis weighing the benefits of the costs of chemoprophylaxis against the benefits of prevention of CAUTI.

Antibiotic resistance is a potentially important complication that could develop with increased antibiotic use for the prevention of CAUTI. Although most studies looked at the type of uropathogen isolated by urine culture, only Baertschi et al. examined the resistance of positive urine cultures to trimethoprim-sulfamethoxazole, and found a higher percentage of uropathogen resistance in the treatment group as compared to placebo. With this in mind, more research is needed on whether the use of prophylactic antibiotics may induce significant resistance in uropathogens. Methenamine is not an antibiotic, but instead is an antiseptic agent that hydrolyses to formaldehyde and ammonia in acidic urine. The combination of hippuric acid, in addition to decreasing urinary pH, also has bacteriostatic effects. The use of methenamine for prophylaxis instead of antibiotics could potentially reduce the rate of antibiotic resistance in prophylaxis for CAUTI. One study in this review noted the presence of fewer opportunistic infections in positive cultures as compared to placebo, and this may be an interesting area for further study of methenamine. Only one randomised control study compared methenamine with antibiotic prophylaxis. This study was small, and did not include the endpoint of symptomatic UTI. In addition, this study used sulphamethizole, which is rarely used alone for prophylaxis or treatment nowadays. Further studies comparing methenamine hippurate to antibiotic prophylaxis would be helpful in determining whether methenamine is equally or more effective than antibiotic use, and whether it would prevent the development of antibiotic resistance.

The strengths of this review include a systematic and comprehensive assessment of published literature, which was performed according to PRISMA guidelines. Though we were unable to perform a meta-analysis due to the considerable heterogeneity between studies, our systematic review indicates that chemoprophylaxis prior to catheter removal is beneficial in gynaecological postoperative patients. Further studies are necessary to define the best agent, dosage, and duration of prophylaxis at catheter removal that would minimise adverse effects, antibiotic resistance, and costs for patients undergoing gynaecologic procedures. Our recommendations for future studies include appropriately powered, randomised controlled studies, comparing an antibiotic (preferably nitrofurantoin) to methenamine hippurate, or comparing a single-dose regimen to a multi-dose regimen, with symptomatic bacteriuria as a primary endpoint. Antibiotic resistance of positive urine cultures and cost-effectiveness should also be examined in order to help us more accurately define a role for chemoprophylaxis in CAUTI prevention after gynaecological procedures.

**CONCLUSION**

Current literature supports chemoprophylaxis with antibiotics or methenamine hippurate for prevention of symptomatic UTI during short-term catheterisation after gynaecologic surgery. Further adequately powered, randomised controlled studies that compare the effectiveness and cost-effectiveness of methenamine hippurate to placebo, or methenamine hippurate to an antibiotic, for the prevention of symptomatic urinary tract infection following short-term catheterisation for gynaecologic surgery, are required.

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**REFERENCES**


