Effective Health Care

Recurrent Urinary Tract Infections in Adult Women

Results of Topic Selection Process & Next Steps

The nominator, the American Urological Association (AUA), is interested in using a new systematic review to inform the creation of a clinical practice guideline for the diagnosis and treatment of recurrent urinary tract infections (UTIs) in adult women. Specifically, the nominator is interested in the natural history of UTIs, including risk factors, prevention, and role of the upper tract; accuracy of diagnostic tests; effectiveness of commonly used treatments; comparative effectiveness of antibiotic and non-antibiotic prophylaxis; effectiveness of interventions to manage side effects; and determining the appropriate endpoint to define treatment success. The nominator's goal is to standardize evaluation and treatment algorithms, decrease the substantial cost associated with the diagnosis and treatment of recurrent UTI, provide guidance regarding antibiotic stewardship, and evaluate treatment options.

Due to limited program resources, the program will not develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Recurrent Urinary Tract Infections in Adult Women

Topic #: 0682

Nomination Date: June 22, 2016

Topic Brief Date: February 10, 2017

Authors:
Stephanie Veazie
Kara Winchell
Rose Relevo
Mark Helfand

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication (Appendix B): A new AHRQ review would not be duplicative of an existing product. Completed and in-process systematic reviews address most but not all of the proposed key questions.
    - We identified 19 completed and/or in-process systematic reviews on anti-infectives (KQ2); diagnostic tests (KQ3); diagnostic tests for asymptomatic bacteriuria (ASB) (KQ4), treatment for recurrent UTIs (KQ6); treatment for ASB (KQ7), and antibiotic prophylaxis (KQ8).
    - We identified no completed or in-process reviews on the natural history of UTIs (KQ1); accuracy of screening urinalysis and chemical strips (KQ5);

interventions for managing side effects (KQ9); or endpoints for evaluating treatment success (KQ10).

- Feasibility: A new AHRQ review is feasible.
    - *Size/scope of the review:* Our search of PubMed resulted in a total of 318 unique titles. Upon title and abstract review, we identified 37 studies potentially relevant to the key questions in the nomination, including 11 studies on the natural history of recurrent UTIs (KQ1); 6 studies on tests for screening, diagnosis, and risk management (KQ3); 1 study on testing for ASB vs. acute bacterial cystitis (KQ4); 1 study on commonly used treatments (KQ6); 2 studies on antibiotic treatments for ASB (KQ7); and 16 studies on prophylaxis (KQ8). We identified no studies on anti-infectives (KQ2), screening urinalysis vs chemical strips (KQ5), interventions for managing side effects (KQ9), or the most appropriate endpoint for evaluating treatment success (KQ10).
    - *Clinicaltrials.gov:* Our search in Clinicaltrials.gov identified 5 ongoing or recently completed studies pertaining to the key questions: 2 studies on the accuracy of tests (KQ3) and 3 studies on prophylaxis (KQ8).
- Impact: The potential for impact for a new AHRQ review is high. Although there is high-quality guidance on this topic, there are concerns that the use of prophylactic antibiotic treatments for recurrent UTIs may lead to antimicrobial resistance, which has increased interest in other options for management. Therefore, there is great interest in synthesizing the most updated evidence on the range of options for prevention and treatments among adult women, which are not comprehensively addressed in available guidance.
- Value: The potential for value for a new AHRQ review is high, as the AUA plans to develop new guidelines on this topic. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

Table of Contents

Introduction

Urinary tract infections are the most common bacterial infection among women; half of all women will acquire a UTI in their lifetime.[1] After an initial UTI, one out of five young women develop a recurrent UTI,[2] defined as two or more infections in six months or three or more infections in one year. Although clinical guidelines (2008)[3] recommend the use of either prophylactic or intermittent antimicrobial therapy or cranberry juice in the management of recurrent UTIs in non-pregnant adult women, there continue to be concerns that the overuse of antibiotics may increase antimicrobial resistance.

Topic nomination *#0682 Recurrent Urinary Tract Infections in Adult Women* was received on June 22, 2016. It was nominated by American Urological Association. We spoke to the nominator to clarify the key questions and PICOs of interest. We removed vaccines for recurrent UTIs from Key Question 2 and Key Question 7, as this intervention is not currently available in the U.S. The questions for this nomination are:

Key Question 1. Among adult women, what is the natural history of recurrent UTIs, including:

a. Rates of recurrence
b. Medical and genetic risk factors
c. Role of upper urinary tract

Key Question 2. Among adult women (with or without a history of recurrent UTIs), what is the effectiveness of anti-infectives (eg, methenamine) for the prevention of recurrent UTIs?

Key Question 3. Among adult women, what is the effectiveness of tests for screening, diagnosis, and risk management of recurrent UTIs?

Key Question 4. Among adult women with suspected recurrent UTIs, what is the accuracy of tests in distinguishing between asymptomatic bacteriuria (ASB) and acute bacterial cystitis?

Key Question 5. Among adult women with suspected recurrent UTIs, what is the comparative effectiveness of screening urinalysis and chemical strips in asymptomatic patients versus assessment at time of symptoms?

Key Question 6. Among adult women with recurrent UTIs, what are the benefits and harms of commonly used treatments?

a. How does the duration of these treatments impact benefits and harms?

Key Question 7. Among adult women, what is the effectiveness of antibiotic treatments for ASB?

Key Question 8. Among adult women with recurrent UTIs, what are the comparative benefits and harms of antibiotic prophylaxis and non-antibiotic prophylaxis treatments?

Key Question 9. Among adult women with recurrent UTIs, what is the effectiveness of interventions for managing side effects and multiple drug resistance associated with available standard therapy (eg, prophylaxis, oral and intravesical antiseptics, oral and intravesical antibiotics, and self-directed programs)?

Key Question 10. Among adult women with recurrent UTIs, what is the most appropriate endpoint for evaluating treatment success?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes, PICOs) of interest. See Table 1.

Table 1. Key Questions and PICOTs $

Key Questions	1. Among adult women, what is the natural history of recurrent UTIs, including: a. Rates of recurrence b. Medical and genetic risk factors c. Role of upper urinary tract	2. Among adult women (with or without a history of recurrent UTIs), what is the effectiveness of anti-infectives (eg, methenamine) for the prevention of recurrent UTIs?	3. Among adult women, what is the comparative effectiveness of tests for screening, diagnosis, and risk management of recurrent UTIs?	4. Among adult women with suspected recurrent UTIs, what is the accuracy of tests in distinguishing between asymptomatic bacteriuria (ASB and acute bacterial cystitis?	5. Among adult women with suspected recurrent UTIs, what is the comparative effectiveness of screening urinalysis and chemical strips in asymptomatic patients versus assessment at time of symptoms?	6. Among adult women with recurrent UTIs, what are the benefits and harms of commonly used treatments? a. How does the duration of these treatments impact benefits and harms?	7. Among adult women, what is the effectiveness of antibiotic treatments for ASB?	8. Among adult women with recurrent UTIs, what are the comparative benefits and harms of antibiotic prophylaxis and non-antibiotic prophylaxis treatments?	9. Among adult women with recurrent UTIs, what is the effectiveness of interventions for managing side effects and multiple drug resistance associated with available standard therapy (eg, prophylaxis, oral and intravesical antiseptics, oral and intravesical antibiotics, and self-directed programs)?	10. Among adult women with recurrent UTIs, what is the most appropriate endpoint for evaluating treatment success?
Population	Adult women with recurrent UTIs	Adult women (with or without a history of recurrent UTIs)	Adult women with recurrent UTIs	Adult women with suspected recurrent UTIs	Adult women with suspected recurrent UTIs	Adult women with recurrent UTIs	Adult women with ASB	Adult women with recurrent UTIs	Adult women with recurrent UTIs	Adult women with recurrent UTIs
Interventions	NA	Anti-infectives (eg, methenamine)	Urine analysis, cutoff values in microbiological studies and antibiotic sensitivities, imaging tests, voiding efficiency (post void residual volumes), cystoscopy, urine culture	Urinalysis, urine cultures	Screening urinalysis or chemical strips, assessment at time of symptoms	Oral and intravesical antiseptics, oral and intravesical antibiotics, self-directed programs	Bladder instillations, intermittent catheterization for impaired bladder emptying with ASB, diabetic control	Vaginal estrogens, probiotics, A-type proanthocyanidins (cranberry products, D-mannose, hyaluronic acid, herbals [e.g., goldenseal and uva ursi], vitamin C, hygiene, contraceptions, fluid intake	Vaginal or oral treatment of secondary fungal infections, cessation of antibiotics prior to course completion due to rash, itching, diarrhea, joint pain, medical intervention including hospitalization for more serious side effects; hematopoietic conditions, such as thrombocytopenia, agranulocytosis as well as SIADH and hyponatremia	Microbiological cure, symptom improvement, reduction of future recurrences, urinary lactoferrin, CRP, interleukin 6, serum procalcitonin, Urinary nitrates and leukocyte esterase.
Comparators	NA	Control (no intervention or placebo)	Other active interventions	NA	Other active interventions	Control (no intervention or placebo)	Control (no intervention or placebo)	Other active interventions	Control (no intervention or placebo)	Other endpoints
Outcomes	Recurrence rates, medical and genetic risk factors, role of upper tract	No or reduced number of UTIs	Diagnostic accuracy, recurrence rates	Sensitivity, specificity, discrimination	Appropriate use of antibiotics, stable antibiotic resistance patterns for coliform organisms, frequency of UTIs	Health care utilization, hospitalization, symptom relief, microbiological outcomes, recurrence rates	Morbidity associated with treatment: of antibiotic side effects (eg, lost work-days, pyelonephritis requiring hospitalization), mortality	Adverse effects, health care utilization, hospitalization, symptom relief, microbiological outcomes and recurrence rates	Reduced side effects, reduced rates of multiple drug resistance	Number of UTIs avoided equated to costs; Number of office and ED visits and hospitalizations avoided equated to costs

Abbreviations: ASB=Asymptomatic Bacteriuria; CRP=C-reactive protein; ED=Emergency Department; NA= Not applicable; UTIs= Urinary Tract Infection

Methods

To assess topic nomination *#0682 Recurrent Urinary Tract Infections in Adult Women* for priority for a systematic review or other AHRQ Effective Health Care (EHC) Program report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. " Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. " Establish the overall *importance* of a potential topic as representing a health or " healthcare issue in the United States. "
3. " Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. " Assess the *potential impact* a new systematic review or other AHRQ product.
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.). See Appendix A.

Feasibility of New Evidence Review

We conducted a literature search in PubMed from July 2011 to July 2016 and identified 318 unique titles. We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We also searched Clinicaltrials.gov for recently completed or in-process unpublished studies. See Table 2, Feasibility Column, Size/Scope of Review Section for the citations of included studies. See Appendix B for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use the information from the proposed evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Urinary tract infections are the most common bacterial infection among women;[1] half of all women will acquire a UTI in their lifetime,[4] and one out of five young women develop a recurrent infection after an initial UTI. UTIs account for 8.1 million visits to health care providers each year.[5]

Desirability of New Review/Duplication

A new AHRQ review would not be duplicative of an existing product. Completed and in-process systematic reviews addressed most but not all of the proposed key questions.

We identified a total of 19 completed and/or in-process systematic reviews, including 1 completed review[6] on anti-infectives (KQ2); 1 completed review[7] on diagnostic tests (KQ3); 1 in-process review[8] on diagnostic tests for asymptomatic bacteriuria (KQ4); 3 completed reviews[7,9,10] on treatment for recurrent UTIs (KQ6); 3 in-process and completed reviews[11-13] on treatments for ASB (KQ7); and 10 in-process and completed reviews[14-23] on antibiotic prophylaxis (KQ8). We identified no completed or in-process reviews on the natural history of UTIs (KQ1); accuracy of screening urinalysis and chemical strips (KQ5); interventions for managing side effects (KQ9); or endpoints for evaluating treatment success (KQ10).

See Table 2, Duplication column for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

The potential for impact of a new AHRQ review is high. Although there is high-quality guidance on this topic,[3,24] there are concerns that the use of prophylactic antibiotic treatments for recurrent UTIs may lead to antimicrobial resistance, which has increased interest in other options for management. Therefore, there is great interest in synthesizing the most updated evidence on the range of options for prevention and treatments among adult women, which are not comprehensively addressed in available guidance.

Feasibility of a New Evidence Review

A new AHRQ evidence review is feasible.

Our search of PubMed resulted in a total of 318 unique titles. Upon title and abstract review, we identified 37 studies potentially relevant to the key questions in the nomination. We identified 11 studies[25-34] on the natural history of recurrent UTIs (KQ1); 6 studies[35-40] on tests for screening, diagnosis, and risk management (KQ3); 1 study[41] on testing for ASB vs. acute bacterial cystitis (KQ4); 1 study[42] on commonly used treatments (KQ6); 2 studies[43,44] on antibiotic treatments for ASB (KQ7); and 16 studies on prophylaxis[45-60] (KQ8). We identified no studies on anti-infectives (KQ2), screening urinalysis vs chemical strips (KQ5), interventions for managing side effects (KQ9), or the most appropriate endpoint for evaluating treatment success (KQ10).

Our search in Clinicaltrials.gov identified 5 ongoing or recently completed studies pertaining to the key questions: 2 studies[61,62] on the accuracy of tests (KQ3) and 3 studies[61-65] on prophylaxis (KQ8).

See Table 2, Feasibility column for the citations that were determined to address the key questions.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
KQ 1. Among adult women, what is the natural history	None identified.	Size/scope of review Relevant Studies Identified: 11

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
of recurrent UTIs, including: a) Rates of recurrence b) Medical and genetic risk factors c) Role of upper urinary tract		• Prospective cohort: 2[25,26] • Retrospective case-control: 6[27-31] • Retrospective cohort: 3[32-34] ClinicalTrials.gov None identified.
KQ 2. Among adult women (with or without a history of recurrent UTIs), what is the effectiveness of anti-infectives (eg, methenamine) for the prevention of recurrent UTIs?	Total number of completed and in-progress systematic reviews: 2 • Cochrane: 1[6]	Size/scope of review Relevant Studies Identified: 0 ClinicalTrials.gov None identified.
KQ 3. Among adult women, what is the comparative effectiveness of tests for screening, diagnosis, and risk management of recurrent UTIs?	Total number of completed and in-progress systematic reviews: 1 • Other: 1[7]	Size/scope of review Relevant Studies Identified: 6 • RCT: 1[35] • Prospective case-control: 1[36] • Prospective cohort: 3[37-39] • Retrospective cohort: 1[40] ClinicalTrials.gov • Completed: 2[61,62]
KQ 4. Among adult women with suspected recurrent UTIs, what is the accuracy of tests in distinguishing between asymptomatic bacteriuria (ASB) and acute bacterial cystitis?	Total number of completed and in-progress systematic reviews: 1 • Other (in process): 1[8]	Size/scope of review Relevant Studies Identified: 1 • RCT: 1[41] ClinicalTrials.gov None identified.
KQ 5. Among adult women with suspected recurrent UTIs, what is the comparative effectiveness of screening urinalysis and chemical strips in asymptomatic patients versus assessment at time of symptoms?	None identified.	Size/scope of review None identified ClinicalTrials.gov None identified.
KQ 6. Among adult women with recurrent UTIs, what are the benefits and harms of commonly used treatments? a. How does the duration of these treatments impact benefits and harms?	Total number of completed and in-progress systematic reviews: 3 • Cochrane: 2[9,10] • Other: 1[7]	Size/scope of review Relevant Studies Identified: 1 • RCT: 1[42] ClinicalTrials.gov None identified.
KQ 7. Among adult women, what is the effectiveness of antibiotic treatments for ASB?	Total number of completed and in-progress systematic reviews: 3 • Cochrane: 2[11,12] • Other (in process): 1[13]	Size/scope of review Relevant Studies Identified: 2 • RCT: 1[43] • Prospective case-control: 1[44] ClinicalTrials.gov None identified.

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
KQ 8. Among adult women with recurrent UTIs, what are the comparative benefits and harms of antibiotic prophylaxis and non-antibiotic prophylaxis treatments?	Total number of completed and in-progress systematic reviews: 10 • Cochrane: 3[14-16] • Other: 2[17,18] • Other (in process): 5[19-23]	Size/scope of review Relevant Studies Identified: 16 • RCTs: 11[45-55] • Prospective cohort: 2[56,57] • Retrospective cohort study: 2[58,59] • Retrospective nested case control: 1[60] ClinicalTrials.gov • Completed: 1[63] • Recruiting: 2[64,65]
KQ 9. Among adult women with recurrent UTIs, what is the effectiveness of interventions for managing side effects and multiple drug resistance associated with available standard therapy (eg, prophylaxis, oral and intravesical antiseptics, oral and intravesical antibiotics, and self-directed programs)?	None identified	Size/scope of review None identified. ClinicalTrials.gov None identified.
KQ 10. Among adult women with recurrent UTIs, what is the most appropriate endpoint for evaluating treatment success?	None identified	Size/scope of review None identified. ClinicalTrials.gov None identified.

Abbreviations: KQ=Key Question; RCT=Randomized Controlled Trial

Value

The potential for value is high, as the AUA plans to develop new guidelines on this topic. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication (Appendix B): A new AHRQ review would not be duplicative of an existing product. Completed and in-process systematic reviews address most but not all of the proposed key questions.
    - We identified 19 completed and/or in-process systematic reviews on anti-infectives (KQ2); diagnostic tests (KQ3); diagnostic tests for asymptomatic bacteriuria (ASB) (KQ4), treatment for recurrent UTIs (KQ6); treatment for ASB (KQ7), and antibiotic prophylaxis (KQ8).
    - We identified no completed or in-process reviews on the natural history of UTIs (KQ1); accuracy of screening urinalysis and chemical strips (KQ5); interventions for managing side effects (KQ9); or endpoints for evaluating treatment success (KQ10).
- Feasibility: A new AHRQ review is feasible.
    - *Size/scope of the review:* Our search of PubMed resulted in a total of 318 unique titles. Upon title and abstract review, we identified 37 studies potentially relevant to the key questions in the nomination, including 11

studies on the natural history of recurrent UTIs (KQ1); 6 studies on tests for screening, diagnosis, and risk management (KQ3); 1 study on testing for ASB vs. acute bacterial cystitis (KQ4); 1 study on commonly used treatments (KQ6); 2 studies on antibiotic treatments for ASB (KQ7); and 16 studies on prophylaxis (KQ8). We identified no studies on anti-infectives (KQ2), screening urinalysis vs chemical strips (KQ5), interventions for managing side effects (KQ9), or the most appropriate endpoint for evaluating treatment success (KQ10).
    - *Clinicaltrials.gov:* Our search in Clinicaltrials.gov identified 5 ongoing or recently completed studies pertaining to the key questions: 2 studies on the accuracy of tests (KQ3) and 3 studies on prophylaxis (KQ8).
- Impact: The potential for impact for a new AHRQ review is high. Although there is high-quality guidance on this topic, there are concerns that the use of prophylactic antibiotic treatments for recurrent UTIs may lead to antimicrobial resistance, which has increased interest in other options for management. Therefore, there is great interest in synthesizing the most updated evidence on the range of options for prevention and treatments among adult women, which are not comprehensively addressed in available guidance.
- Value: The potential for value for a new AHRQ review is high, as the AUA plans to develop new guidelines on this topic. This organization has previously produced high-quality evidence-based guidelines, and is transparent about its methodology.

References (

1. " Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Mar 1 2011;52(5):e103-120.
2. " Tolkoff-Rubin NE CR, Rubin RH. . Urinary tract infection, pyelonephritis, and reflux nephropathy. *Brenner & Rector's The Kidney. 8th ed. .* Vol 2. Philadelphia: Saunders; 2008:1203–1238.
3. " National Guideline Clearinghouse (NGC). Guideline summary: Treatment of urinary tract infections in nonpregnant women. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2008 Mar 01. Reaffirmed 2012. Available: https://www.guideline.gov.
4. " TL G. Urinary tract infection in women. In: Department of Health and Human Services PHS, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, ed. Washington DC2007.
5. " Schappert SM RE. Ambulatory medical care utilization estimates for 2006. . *National Center for Health Statistics* 2008;http://www.cdc.gov/nchs/data/nhsr/nhsr008.pdf .
6. " Lee BSB, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database of Systematic Reviews.* 2012(10).
7. " Grigoryan L, Trautner BW, Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: A review. *JAMA.* 2014;312(16):1677-1684.
8. " Rogozinska E, Formia, S, Khan K. Accuracy of tests to detect asymptomatic bacteriuria in antenatal care settings: a systematic review *PROSPERO International prospective register of systematic reviews* 2015; Anticipated completion Feb 2016:http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027905.
9. " Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database of Systematic Reviews.* 2011(1).
10. " Flower A, Wang L-Q, Lewith G, Liu JP, Li Q. Chinese herbal medicine for treating recurrent urinary tract infections in women. *Cochrane Database of Systematic Reviews.* 2015(6).
11. " Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database of Systematic Reviews.* 2015(8).
12. " Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database of Systematic Reviews.* 2015(11).
13. " Koves B, Pickard, R, Wullt, B, Cai, T, Hofmann, F Systematic review on the management of asymptomatic bacteriuria 2015; http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015016457.
14. " Schneeberger C, Geerlings SE, Middleton P, Crowther CA. Interventions for preventing recurrent urinary tract infection during pregnancy. *Cochrane Database of Systematic Reviews.* 2015(7).
15. " Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews.* 2012(10).
16. " Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. *Cochrane Database of Systematic Reviews.* 2015(12).
17. " Beerepoot MA, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol.* Dec 2013;190(6):1981-1989.
18. " Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE. Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. *Can J Urol.* Feb 2013;20(1):6607-6614.

19. " Kern C, Liska, D. Meta-analysis of cranberry and recurrent urinary tract infections (UTIs) in generally healthy women 2015; http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024439.
20. " Koves B, Pickard, R, Wullt, B, Wagenlehner, F, Veeratterapillay, R. Prevention of recurrent urinary tract infection in women: systematic review 2015; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029688
21. " Price J, McDonagh, M, Gregory, W, Guran, L. Nitrofurantoin versus other prophylactic agents in reducing recurrent urinary tract infections in adult women: a systematic review 2015; http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015023966.
22. " Ahmed H, Davies, F, Francis, N, Farewell, D, Butler, C. Long-term antibiotics for preventing recurrent urinary tract infections in older adults: protocol for a systematic review 2015; http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015016628.
23. " Wang CH, Fang CC, Chen NC, et al. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med.* Jul 9 2012;172(13):988-996.
24. " Arnold JJ, Hehn LE, Klein DA. Common Questions About Recurrent Urinary Tract Infections in Women. *American family physician.* Apr 01 2016;93(7):560-569.
25. " Golebiewska J, Debska-Slizien A, Komarnicka J, Samet A, Rutkowski B. Urinary tract infections in renal transplant recipients. *Transplantation proceedings.* Oct 2011;43(8):2985-2990.
26. " Golebiewska JE, Debska-Slizien A, Rutkowski B. Urinary tract infections during the first year after renal transplantation: one center's experience and a review of the literature. *Clinical transplantation.* Nov 2014;28(11):1263-1270.
27. " Hisano M, Bruschini H, Nicodemo AC, Gomes CM, Lucon M, Srougi M. The Bacterial Spectrum and Antimicrobial Susceptibility in Female Recurrent Urinary Tract Infection: How Different They Are From Sporadic Single Episodes? *Urology.* Sep 2015;86(3):492-497.
28. " Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract.* Sep 2012;66(9):891-896.
29. " Chuang FC, Kuo HC. Increased urothelial cell apoptosis and chronic inflammation are associated with recurrent urinary tract infection in women. *PLoS One.* 2013;8(5):e63760.
30. " Fu AZ, Iglay K, Qiu Y, Engel S, Shankar R, Brodovicz K. Risk characterization for urinary tract infections in subjects with newly diagnosed type 2 diabetes. *J Diabetes Complications.* Nov-Dec 2014;28(6):805-810.
31. " Espinar MJ, Miranda IM, Costa-de-Oliveira S, Rocha R, Rodrigues AG, Pina-Vaz C. Urinary Tract Infections in Kidney Transplant Patients Due to Escherichia coli and Klebsiella pneumoniae-Producing Extended-Spectrum beta-Lactamases: Risk Factors and Molecular Epidemiology. *PloS one.* 2015;10(8):e0134737.
32. " Bodro M, Sanclemente G, Lipperheide I, et al. Impact of antibiotic resistance on the development of recurrent and relapsing symptomatic urinary tract infection in kidney recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* Apr 2015;15(4):1021-1027.
33. " Camargo LF, Esteves AB, Ulisses LR, Rivelli GG, Mazzali M. Urinary tract infection in renal transplant recipients: incidence, risk factors, and impact on graft function. *Transplantation proceedings.* Jul-Aug 2014;46(6):1757-1759.
34. " Puntis D, Malik S, Saravanan V, et al. Urinary tract infections in patients with rheumatoid arthritis. *Clin Rheumatol.* Mar 2013;32(3):355-360.
35. " Holm A, Cordoba G, Sorensen TM, Jessen LR, Siersma V, Bjerrum L. Point of care susceptibility testing in primary care - does it lead to a more appropriate prescription of antibiotics in patients with uncomplicated urinary tract infections? Protocol for a randomized controlled trial. *BMC family practice.* 2015;16:106.

36. " Bulut IK, Mir S, Berdeli A, Sozeri B. The predictive value of urinary UPIb mRNA levels in VUR and recurrent urinary tract infections. *Clin Nephrol.* Mar 2014;81(3):152-158.
37. " Howles S, Tempest H, Doolub G, et al. Flexible cystoscopy findings in patients investigated for profound lower urinary tract symptoms, recurrent urinary tract infection, and pain. *J Endourol.* Nov 2012;26(11):1468-1472.
38. " Lo TS, Khanuengkitkong S, Tan YL, Dass AK, Wu PY, Al-Kharabsheh AM. Low incidence of bacteriuria with outpatient flexible cystoscopy. *Aust N Z J Obstet Gynaecol.* Aug 2014;54(4):366-370.
39. " Rodrigues P, Hering F, Campagnari JC. Involuntary detrusor contraction is a frequent finding in patients with recurrent urinary tract infections. *Urol Int.* 2014;93(1):67-73.
40. " Johnson JD, O'Mara HM, Durtschi HF, Kopjar B. Do urine cultures for urinary tract infections decrease follow-up visits? *J Am Board Fam Med.* Nov-Dec 2011;24(6):647-655.
41. " Beerepoot MA, den Heijer CD, Penders J, Prins JM, Stobberingh EE, Geerlings SE. Predictive value of Escherichia coli susceptibility in strains causing asymptomatic bacteriuria for women with recurrent symptomatic urinary tract infections receiving prophylaxis. *Clin Microbiol Infect.* Apr 2012;18(4):E84-90.
42. " Ejrnaes K, Stegger M, Reisner A, et al. Characteristics of Escherichia coli causing persistence or relapse of urinary tract infections: phylogenetic groups, virulence factors and biofilm formation. *Virulence.* Nov-Dec 2011;2(6):528-537.
43. " Minardi D, Pellegrinelli F, Conti A, et al. alpha1-Blockers for the treatment of recurrent urinary tract infections in women with dysfunctional voiding: a prospective randomized study. *Int J Urol.* Jan 2015;22(1):115-121.
44. " Cai T, Mazzoli S, Mondaini N, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? *Clin Infect Dis.* Sep 2012;55(6):771-777.
45. " Beerepoot MA, ter Riet G, Nys S, et al. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. *Arch Intern Med.* Jul 25 2011;171(14):1270-1278.
46. " Beerepoot MA, ter Riet G, Nys S, et al. Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med.* May 14 2012;172(9):704-712.
47. " Bosmans JE, Beerepoot MA, Prins JM, ter Riet G, Geerlings SE. Cost-effectiveness of cranberries vs antibiotics to prevent urinary tract infections in premenopausal women: a randomized clinical trial. *PLoS One.* 2014;9(4):e91939.
48. " Costantini E, Zucchi A, Salvini E, et al. Prulifloxacin vs fosfomycin for prophylaxis in female patients with recurrent UTIs: a non-inferiority trial. *Int Urogynecol J.* Sep 2014;25(9):1173-1178.
49. " Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol.* Feb 2014;32(1):79-84.
50. " Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc.* Feb 2012;87(2):143-150.
51. " Takahashi S, Hamasuna R, Yasuda M, et al. A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. *J Infect Chemother.* Feb 2013;19(1):112-117.
52. " Vostalova J, Vidlar A, Simanek V, et al. Are High Proanthocyanidins Key to Cranberry Efficacy in the Prevention of Recurrent Urinary Tract Infection? *Phytother Res.* Oct 2015;29(10):1559-1567.
53. " Wagenlehner FM, Ballarini S, Pilatz A, Weidner W, Lehr L, Naber KG. A Randomized, Double-Blind, Parallel-Group, Multicenter Clinical Study of Escherichia coli-Lyophilized Lysate for the Prophylaxis of Recurrent Uncomplicated Urinary Tract Infections. *Urol Int.* 2015;95(2):167-176.

54. " Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ.* 2015;351:h6544.
55. " Gagyor I, Hummers-Pradier E, Kochen MM, Schmiemann G, Wegscheider K, Bleidorn J. Immediate versus conditional treatment of uncomplicated urinary tract infection - a randomized-controlled comparative effectiveness study in general practices. *BMC Infect Dis.* 2012;12:146.
56. " Burleigh AE, Benck SM, McAchran SE, Reed JD, Krueger CG, Hopkins WJ. Consumption of sweetened, dried cranberries may reduce urinary tract infection incidence in susceptible women--a modified observational study. *Nutr J.* 2013;12(1):139.
57. " Sanchez Ballester F, Ruiz Vidal V, Lopez Alcina E, et al. Cysticlean(R) a highly pac standardized content in the prevention of recurrent urinary tract infections: an observational, prospective cohort study. *BMC Urol.* 2013;13:28.
58. " Lorenzo-Gomez MF, Padilla-Fernandez B, Garcia-Cenador MB, et al. Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections. *Front Cell Infect Microbiol.* 2015;5:50.
59. " Lorenzo-Gomez MF, Padilla-Fernandez B, Garcia-Criado FJ, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics. *Int Urogynecol J.* Jan 2013;24(1):127-134.
60. " Ciani O, Arendsen E, Romancik M, et al. Intravesical administration of combined hyaluronic acid (HA) and chondroitin sulfate (CS) for the treatment of female recurrent urinary tract infections: a European multicentre nested case-control study. *BMJ open.* 2016;6(3):e009669.
61. " Healthy.io Ltd. Method Comparison & User Performance Study. *ClinicalTrials.gov.* 2016;NCT02785445.
62. " University of Copenhagen. Effect of a Diagnostic Algorithm for Urinary Tract Infection in General Practice. *ClinicalTrials.gov.* 2016;NCT02698332.
63. " Danone Research. The Effect of Increased Water Intake on the Frequency of the Clinical Recurrent Urinary Tract Infections in Pre-menopausal Women: S-HYDRACYST (S-HYDRACYST). *ClinicalTrials.gov.* 2016;NCT02444975.
64. " University of California, San Diego. Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women (VESPR). *ClinicalTrials.gov.* 2016;NCT01958073.
65. " Hatalova K, Pella D, Sidlo R, Hatala R. Switching from a Free Association of Perindopril/Amlodipine to a Fixed-Dose Combination: Increased Antihypertensive Efficacy and Tolerability. *Clin Drug Investig.* Jul 2016;36(7):591-598.
66. " Fenwick EA, Briggs AH, Hawke CI. Management of urinary tract infection in general practice: a cost-effectiveness analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners.* Aug 2000;50(457):635-639.

Appendices

Appendix A: Selection Criteria Summary (

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary (

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents health care drugs and interventions available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Urinary tract infections (UTIs) are the most common bacterial infection among women;[1] half of all women will acquire a UTI in their lifetime,[4] and one out of five young women develop a recurrent infection after an initial UTI.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this topic addresses both benefits and potential harms of treatments for recurrent UTIs.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this topic represents high costs due to common use. UTIs account for 8.1 million visits to health care providers each year.[5]
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new AHRQ review would not be duplicative of an existing product. Completed and in-process systematic reviews address most but not all of the proposed key questions. We identified a total of 19 completed and/or in-process systematic reviews, including 1 completed review[6] on anti-infectives (KQ2); 1 completed review[7] on diagnostic tests (KQ3); 1 in-process review[8] on diagnostic tests for asymptomatic bacteriuria (KQ4); 3 completed reviews[7,9,10] on treatment for recurrent UTIs (KQ6); 3 in-process and completed reviews[11-13] on treatments for ASB (KQ7); and 10 in-process and completed reviews[14-23] on antibiotic prophylaxis (KQ8). We identified no completed or in-process

	reviews on the natural history of UTIs (KQ1); accuracy of screening urinalysis and chemical strips (KQ5); interventions for managing side effects (KQ9); or endpoints for evaluating treatment success (KQ10).
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Although the standard of care is clear based on high-quality guidance,[3,24] there are concerns about that the use of prophylactic antibiotics for treating UTIs may lead to increased anti-microbial resistance. Therefore, there is great interest in synthesizing the most updated evidence on the range of options for prevention and treatments among adult women, which are not comprehensively addressed in available guidance.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is considerable practice variation on this topic.[66]
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new AHRQ review is feasible. *Size/scope of the review:* Our search of PubMed resulted in a total of 318 unique titles. Upon title and abstract review, we identified 37 studies potentially relevant to the key questions in the nomination. We identified 11 studies[25-34] on the natural history of recurrent UTIs (KQ1); 6 studies[35-40] on tests for screening, diagnosis, and risk management (KQ3); 1 study[41] on testing for ASB vs. acute bacterial cystitis (KQ4); 1 study[42] on commonly used treatments (KQ6); 2 studies[43,44] on antibiotic treatments for ASB (KQ7); and 16 studies on prophylaxis[45-60] (KQ8). We identified no studies on anti-infectives (KQ2), screening urinalysis vs chemical strips (KQ5), interventions for managing side effects (KQ9), or the most appropriate endpoint for evaluating treatment success (KQ10). *Clinicaltrials.gov:* Our search in Clinicaltrials.gov identified 5 ongoing or recently completed studies pertaining to the key questions: 2 studies[61,62] on the accuracy of tests (KQ3) and 3 studies[61-65] on prophylaxis (KQ8).
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic exists within a clinical context that is amenable to evidence-based change.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the American Urological Association plans to develop guidelines on the diagnosis, prevention and treatment of recurrent UTIs.

Abbreviations: ASB= Asymptomatic bacteriuria; AHRQ= Agency for Healthcare Research and Quality; KQ=Key Question; UTI=Urinary Tract Infection

Appendix B. Search Strategy & Results (Feasibility) !

Topic: Recurrent UTI Date: July 21, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Recurrent Urinary Tract Infection Etiology History Classification Prevention and control Diagnosis Therapy	((("Urinary Tract Infections/classification"[Mesh] OR "Urinary Tract Infections/diagnosis"[Mesh] OR "Urinary Tract Infections/etiology"[Mesh] OR "Urinary Tract Infections/history"[Mesh] OR "Urinary Tract Infections/prevention and control"[Mesh] OR "Urinary Tract Infections/therapy"[Mesh]))) AND recurrent[Title/Abstract]
NOT	
Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; Human ; English	Filters activated: published in the last 5 years, Humans, English
N=318	
Systematic Review N=23	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials N=134	Cochrane Sensitive Search Strategy for RCT’s “(((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other N=161	

ClinicalTrials.gov searched on July 21, 2016

Results for Studies Currently Recruiting
78 studies found for: Recruiting | Urinary Tract Infections | Studies received from 07/21/2011 to 07/21/2016
https://clinicaltrials.gov/ct2/results?term=&recr=Recruiting&type=&rslt=&age_v=&gndr=&cond=Urinary+Tract+Infections&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=07%2F21%2F2011&rcv_e=07%2F21%2F2016&lup_s=&lup_e=

Results for Closed Studies – Active, not recruiting
4 studies found for: Active, not recruiting | Urinary Tract Infections | Studies received from 07/21/2011 to 07/21/2016
https://clinicaltrials.gov/ct2/results?term=&recr=Active%2C+not+recruiting&type=&rslt=&age_v=&gndr=&cond=Urinary+Tract+Infections&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=07%2F21%2F2011&rcv_e=07%2F21%2F2016&lup_s=&lup_e=

Results for Closed Studies – Completed
60 studies found for: Completed | Urinary Tract Infections | Studies received from 07/21/2011 to 07/21/2016

https://clinicaltrials.gov/ct2/results?term=&recr=Completed&type=&rslt=&age_v=&gndr=&cond=Urinary+Tract+Infections&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=07%2F21%2F2011&rcv_e=07%2F21%2F2016&lup_s=&lup_e=