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Comparative effectiveness of treatments for asymptomatic bacteriuria including watchful waiting

Prepared for:
Patient-Centered Outcomes Research Institute (PCORI)
1828 L St., NW, Suite 900
Washington, DC 20036
Phone: (202) 827-7700
Fax: (202) 355-9558
www.pcori.org

Prepared by:
Johns Hopkins Evidence-Based Practice Center
Baltimore, Maryland

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PCORI Scientific Program Area:

Comparative Effectiveness Research

Executive Summary

Overall Comparative Research Question

What is the comparative effectiveness of treatments (antibiotics, etc) for asymptomatic bacteriuria including watchful waiting?

Brief Overview of the Topic

Asymptomatic bacteriuria occurs when specific bacteria are present in the urine, without signs or symptoms of a urinary tract infection. Guidelines consistently recommend screening and treatment of asymptomatic bacteriuria in pregnant women. Some, but not all guidelines, recommend screening and treatment prior to urologic and urogynecologic procedures. Other populations, especially those in long-term care facilities and with urinary catheters, are screened despite the absence of guideline recommendations. Concerns have been raised that screening for asymptomatic bacteriuria may lead to overuse of antibiotics, which may contribute to antibiotic resistance.

Impact on Health and Populations

Asymptomatic bacteriuria is more common among women, older individuals, residents of long-term care facilities, people with indwelling urinary catheters, and those with diabetes mellitus, spinal cord injuries or who are undergoing hemodialysis.

Assessment of Current Options

In current clinical practice, individuals who are screened and test positive for asymptomatic bacteriuria often are prescribed antibiotics. However, clinicians may choose not to use antibiotics until symptoms occur which is called watchful waiting. Other terms for watchful waiting are expectant management or active surveillance.

Likelihood of Implementation of Research Results in Practice

The results are likely to be implemented in practice, but the interventions needed to promote adherence may be resource intensive because of the need to change long-standing behaviors. For example, an audit and feedback intervention by the United States Department of Veterans Affairs aimed to improve the capacity of internal medicine residents and long-term care personnel to distinguish between asymptomatic bacteriuria and catheter-associated urinary tract infection. The intervention included one on one feedback for each of the 169 providers with a slide presentation for each case of asymptomatic bacteriuria treated by each provider.[1, 2] After one year of one on one case review and one year of ward-level feedback (instead of individual) the overtreatment rate decreased from 1.6 to 0.5 per 1,000 bed-days. In the control group which received copies of the guidelines and no individual feedback, the overtreatment rate decreased from 0.5 to 0.4 per 1,000 bed-days.

Durability of Information

The information is likely to be relevant for years to come. Antibiotic resistance is likely to remain a concern. As a greater proportion of the population is affected by diabetes mellitus and spends periods of time in long-term care and skilled nursing facilities, the population at risk of overscreening and overtreatment for asymptomatic bacteriuria is likely to grow.

Comparative effectiveness of treatments for asymptomatic bacteriuria including watchful waiting

1. Contributors

Susan Hutfless, PhD, Johns Hopkins University School of Medicine, Department of Medicine, Division of Gastroenterology, and Evidence based Practice Center
Jenell S, Coleman, MD, Johns Hopkins University School of Medicine, Department of Gynecology and Obstetrics
Geetika Sood, MD, Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases
Catalina Suarez-Cuervo, MD, Johns Hopkins University Bloomberg School of Public Health, Evidence based Practice Center
Eric B, Bass, MD, MPH, Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Evidence based Practice Center

2. Introduction

Asymptomatic bacteriuria occurs when specific bacteria are present in the urine without signs or symptoms of a urinary tract infection. Asymptomatic bacteriuria can also be referred to as asymptomatic urinary infection.[3] Asymptomatic bacteriuria is more common among women, older individuals, residents of long-term care facilities, people with indwelling urinary catheters, and those with diabetes mellitus, spinal cord injuries or who are undergoing hemodialysis (Table 1).

The Infectious Diseases Society of America (IDSA) *Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults*[3] and the U.S. Preventive Services Task Force (USPSTF) *Screening for Asymptomatic Bacteriuria in Adults: Evidence for the U.S. Preventive Services Task Force Reaffirmation Recommendation Statement*[4] recommend specific populations that should be screened for asymptomatic bacteriuria (Table 1). The World Health Organization (WHO) provides treatment recommendations for pregnant women.[5]

Table 1. Guidelines for the Treatment of Asymptomatic Bacteriuria

Guideline	Recommendations for Screening	Recommendations for Treatment	Recommendations against Screening or Treatment
IDSA[3]	Pregnant women Screening at least once in early pregnancy, (A-I). Periodic screening for recurrent bacteriuria in pregnant women should be undertaken following therapy (A-III). Urological procedures Screening and treatment of asymptomatic bacteriuria before transurethral resection of the prostate (A-I). Screening and treatment before urologic procedures for which mucosal bleeding is anticipated (A-III).	Pregnant women Pregnant women should be treated if the results are positive (A-I). The duration of antimicrobial therapy should be 3–7 days (A-II). Urological procedures Before transurethral resection of the prostate. Antimicrobial therapy should be initiated shortly before the procedure (A-II). Antimicrobial therapy should not be continued after the procedure, unless an indwelling catheter remains in place (B-II). Indwelling catheter Antimicrobial treatment may be considered for asymptomatic women with catheter-acquired bacteriuria that persists 48 hours after indwelling catheter removal (B-I).	Pregnant women No recommendation can be made for or against repeated screening of culture-negative women in later pregnancy (No evidence grading) Urologic conditions • Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment (A-II). • Catheterized patients while the catheter remains place (A-I). Transplant recipients No recommendation can be made for screening for or treatment of asymptomatic bacteriuria in renal transplant or other solid organ (C-III). Other populations Premenopausal and non-pregnant women (A-I); diabetic women* (A-I); elderly and other institutionalized people (A-I); older people living in the community (A-II); and people with spinal cord injury (A-II).

Guideline	Recommendations for Screening	Recommendations for Treatment	Recommendations against Screening or Treatment
WHO[5]		Pregnant women Antibiotic treatment for asymptomatic bacteriuria in pregnant women is recommended based on the results of a Cochrane review.[6]	
USPSTF[4]	Pregnant women Screening for asymptomatic bacteriuria with urine culture for pregnant women at 12 to 16 weeks gestation or at their first prenatal visit (Grade A)		The USPSTF recommends against screening for asymptomatic bacteriuria in men and non-pregnant women (Grade D)

Grade A: high certainty that the net benefit is substantial
A-I: Good evidence to support a recommendation for use; Evidence from at least one properly randomized, controlled trial
A-II: Good evidence to support a recommendation for use; Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies [preferably from more than one center]; from multiple time-series; or from dramatic results from uncontrolled experiments
A-III: Good evidence to support a recommendation for use; Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
B-I: Moderate evidence to support a recommendation for use; Evidence from at least one properly randomized, controlled trial
B-II: Moderate evidence to support a recommendation; Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies [preferably from more than one center]; from multiple time-series; or from dramatic results from uncontrolled experiments
C-III: Poor evidence to support a recommendation; Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Grade D: moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits
*Guidelines are specific for diabetic women, as diabetic men do not appear to have an increased prevalence of bacteriuria, compared with nondiabetic men

The American Academy of Family Physicians, American Urological Association, and the Healthcare Infection Control Practices Advisory Committee guidelines reaffirm the recommendations of the IDSA, USPSTF and WHO. [3,7,8] The American College of Obstetricians and Gynecologists (ACOG) also reaffirms IDSA recommendations for pregnant, non-pregnant, menopausal and diabetic women,[9] but recommends screening for asymptomatic bacteriuria before all urogynecologic surgical procedures (as opposed to IDSA which restricted to procedures where mucosal bleeding is anticipated) and to treat positive results. ACOG's rationale for screening and treatment is that bacteriuria or infection can cause detrusor instability, also called overactive bladder, after the procedure. [10]

The IDSA guidelines are currently being updated with a projected publication in Fall 2017.[11] The USPSTF recommendations are not currently being updated.[12]

3. Methods

Literature search:

We conducted a literature search to identify reports around the treatment of asymptomatic bacteriuria. We searched the Cochrane Database of Systematic Reviews, the Agency for Healthcare Research and Quality's website, and PubMed for recent systematic reviews. We searched the websites for government agencies, such as the CDC, the NIH, and relevant professional associations and societies (i.e. the Infectious Diseases Society of America, The American Urological Association, The American Congress of Obstetricians and Gynecologists, the U.S. Preventive Services Task Force, the World Health Organization, the UK National Institute for Health and Care Excellence, and the American Association of Family Practitioners) for practice guidelines and reports that contain data on the disease burden and impact of the condition on the population, as well as any references or sites suggested by our experts.

Ongoing studies:

We searched clinicalTrials.gov on September 8th, 2016 for studies relevant to the topic. We used the broad search terms "asymptomatic bacteriuria".

We searched NIH reporter (https://projectreporter.nih.gov/reporter.cfm) and the PCORI's funded research database (http://www.pcori.org/research-results) for studies and awards relevant to the topic.

The results of these searches are described in the report.

Experts

We had two experts involved in the development of the brief. Dr. Coleman, from the Department of Gynecology and Obstetrics and Dr. Sood, from the Division of Infectious Diseases. Both experts helped us frame the topic, pointed us to relevant literature and helped us identify the main research gaps and potential research questions. We also had the perspective of an internist and primary care physician expert from Dr. Eric Bass, our task leader.

4. Symptoms and Patient-Centered Outcomes

By definition, asymptomatic bacteriuria has no symptoms. Distinguishing between asymptomatic bacteriuria and urinary tract infection can be difficult. Symptoms of urinary tract infection include fever or chills, dysuria (pain or discomfort on urinating), frequency, urgency, new-onset or worsening incontinence, foul odor, and suprapubic or flank pain. These symptoms are not specific to urinary tract infection and may lead to misclassification of asymptomatic bacteriuria as a

urinary tract infection. Elderly individuals and those with baseline impaired cognition or extensive comorbidities are at higher risk of these symptoms and may have decreased cognitive ability to be able to describe these symptoms. These same populations are often at higher risk of side effects from the broad-spectrum antibiotics used to treat asymptomatic bacteriuria.[13]

Pregnant women with untreated asymptomatic bacteriuria are at increased risk of having lower birth weight and pre-term babies,[5] and infections that could put their babies at risk such as chorioamnionitis (bacterial infection of the fetal membranes) and pyelonephritis (kidney infection).[14] The guidelines consistently recommend screening and treatment in pregnant women to prevent these established outcomes. Short and long terms outcomes of treating versus not treating asymptomatic bacteriuria in other individuals are not well established.

Watchful waiting is the preferred treatment for the majority of non-pregnant patients with asymptomatic bacteriuria. Patients who receive treatment for asymptomatic bacteriuria have a higher risk of recurrent urinary tract infections and kidney infections, although the decision to treat may be influenced by other factors that are impacting the risk of these outcomes (*i.e.,* confounding by indication).[15]

Patients who test positive for asymptomatic bacteriuria who are not offered treatment with antibiotics may worry about the lack of treatment. Most people in the U.S. are familiar with antibiotics and consider them to be safe. The social, economic and political implications of antibiotic treatment and microbial resistance are growing in importance at the national and international levels.[16, 17]

5. Impact/Burden of the Condition

Asymptomatic bacteriuria is more common in women and older persons. Individuals are particularly vulnerable to asymptomatic bacteriuria if they have indwelling catheters, spinal cord injuries, diabetes mellitus, hemodialysis, or reside in a long-term care facility (Table 2).

Pregnant women with diabetes have a higher risk of developing asymptomatic bacteriuria and urinary tract infections because their urinary tract contracts more slowly to move urine down (called peristalsis) and urine has more sugar than it normally should (called glucosuria)[18] Pregnant women who take sodium-glucose co-transporter 2 (SGLT-2) inhibitors to control their diabetes may be at a greater risk because of the glucosuria associated with this treatment.[19] It is important to determine whether women with diabetes mellitus should have a different monitoring regimen

for asymptomatic bacteriuria than other pregnant women because of their greater risk of asymptomatic bacteriuria and their higher risk of pregnancy complications.

Table 2. Prevalence of Asymptomatic Bacteriuria in the United States[3]

Population	Prevalence, %
Women	
Healthy, premenopausal women	1.0–5.0
Pregnant women	1.9–9.5
Postmenopausal women aged 50–70 years	2.8–8.6
Diabetes mellitus	
Women	9.0–27
Men	0.7–11
Elderly persons in the community	
Women	10.8–16
Men	3.6–19
Elderly persons in a long-term care facility	
Women	25–50
Men	15–40
Patients with spinal cord injuries and Intermittent catheter use	23–89
Patients undergoing hemodialysis	28
Patients with indwelling catheter use	
Short-term	9–23
Long-term	100

Asymptomatic bacteriuria is more common among individuals with diabetes mellitus. A recent meta-analysis of 22 studies reported a higher prevalence of asymptomatic bacteriuria in individuals with diabetes compared to those without diabetes considered healthy controls (12.2% vs 4.5%). Asymptomatic bacteriuria is more common in both type 1 diabetes (odds ratio (OR) 3.0; 95% confidence interval (CI) 1.1-8.0) and type 2 diabetes (OR 3.2; 95% CI 2.0-5.2). [20]

Asymptomatic bacteriuria is very common among hospitalized individuals and residents of long-term care facilities. The presence of a urinary catheter allows bacteria to colonize the catheter and accumulate, with a prevalence of 9–23% in short-term and 100% in long-term catheterization. There is no difference between treatment and no treatment in mortality, costs, or rates of symptomatic urinary tract infections, *Clostridium difficile* infections, or antimicrobial

resistant strains.[21] In 2001, a consensus conference was held to define what today is known as "the Loeb minimum criteria for initiation of antibiotics in residents of long term care facilities."[22] According to these criteria, the smell and appearance of the urine are not a valid indication for treatment. The Loeb guidelines have not been tested in a randomized comparative study and are not routinely used in practice.[23] The minimum criteria for initiating antibiotics for urinary tract infections in residents without an indwelling urinary catheter include:

- Acute dysuria alone; or
- Fever greater than 37.9°C or 1.5°C increase above baseline temperature and at least one of the following new or worsening findings: urgency, frequency, suprapubic pain, gross hematuria, costovertebral tenderness, and urinary incontinence.

No data are available on the differences in the prevalence of asymptomatic bacteriuria by race, location or income. For symptomatic bacteriuria, no racial or ethnicity differences were found in the rates of potentially preventable hospitalizations due to urinary tract infections.[24]

No information is available on the direct costs of asymptomatic bacteriuria. The risks of treating asymptomatic bacteriuria are predominately side-effects of antibiotics at the individual level and the development of antibiotic resistance and tolerance at the population-level.[25] There is a general concern in medicine about overuse of antibiotics.[26] Despite recommendations against antibiotic treatment for asymptomatic bacteriuria in non-pregnant women, clinicians are still prescribing antibiotics in special populations like those with diabetes mellitus, elderly patients, and those in the inpatient setting and long-term facilities, raising concern about incorrect prescriptions, rising costs, and infections with Clostridium difficile or multi-drug resistant organisms.[27, 28]

6. Evidence Gaps

No consensus exists on which antibiotic is preferred when treatment with antibiotics is indicated.

No recommendations are available on which antibiotic is preferred for the treatment of asymptomatic bacteriuria when treatment with antibiotics is indicated. Nitrofurantoin or trimethoprim-sulfamethoxazole (TMP/SMX) may be as effective at clearing the bacteria as fluoroquinolones, amoxicillin and ampicillin, broad-spectrum antibiotics that are associated with resistance to bacteria that grow in the urinary tract.[13]

No consensus exists on how to prevent inappropriate screening for asymptomatic bacteriuria. Despite IDSA and USPSTF guidelines, chronically ill patients, those in long-term facilities, and those with indwelling catheters have frequent urine cultures which prompt unnecessary treatment. Better communication, education and guidance for healthcare workers, patients and families to reduce the high rate of screening could lead to lower rates of diagnosis and subsequent overtreatment.[29-31]

When antibiotic treatment is withheld, it is unclear what should be recommended as part of a watchful waiting strategy. If watchful waiting (also known as expectant management) is recommended, it is unclear when the patient should return for follow-up or testing. Evidence is needed to determine what symptoms should prompt the patient to contact the health care facility for testing or treatment. Not treating documented asymptomatic bacteriuria could have legal implications if the patient later develops a severe urinary tract infection. Efforts to improve communication about the guidelines should consider addressing the legal implications of adherence with guidelines.

A**lternatives to antibiotics have not been compared directly with antibiotics for asymptomatic bacteriuria.**

Cranberries. Cranberries and cranberry juice have been used as treatment of symptomatic bacteriuria and prevention of urinary tract infections.[32-34] However, a 2012 Cochrane systematic review that included 24 studies and 4473 patients concluded that cranberry products did not significantly reduce urinary tract infections in the general population and populations at risk.[35]

Bladder microbiota: The healthy bladder is not sterile. Therefore, instead of talking about asymptomatic bacteriuria, perhaps the research community should be referring to "dysbiosis" with an aim to understanding the perturbation of the normal bacterial community of the bladder and the normal range of urinary microbiota states among groups of women (*e.g.,* by age, hormonal status, race, and ethnicity).[36] It is possible that studies of the bladder microbiota or microbiome may result in treatments to modify the microbiota as alternatives to antibiotics.[37] Some nonpathogenic strains of *E. coli* are under investigation for use in preventing urinary tract infections.[38] Some strains of *E. coli* appear to have an analgesic effect and relieve the pelvic pain caused by the urinary tract infection.[39] These strains have not been tested in the setting of asymptomatic bacteriuria.

7. Ongoing Research

We searched the websites of ClinicalTrials.gov, NIH Reporter and PCORI to identify ongoing research.

ClinicalTrials.gov results

We searched clinicalTrials.gov on September 8, 2016. A total of 29 studies were found when we searched the listed condition to contain "asymptomatic bacteriuria." Seven studies were not relevant because they included only patients with urinary tract infections and not asymptomatic bacteriuria. Fifteen studies were relevant.

Guideline adherence

- NCT01052545: Asymptomatic Bacteriuria Guideline Implementation Study.[2]
    - This study examined implementation with guidelines using personalized audit-feedback versus distributing copies of guidelines.[1, 40]The patients of Veterans Affairs healthcare providers who received audit-feedback received fewer urine cultures, but had no difference in over-treatment (0.4 vs 0.5 treatments/1000 bed-days) or undertreatment (0.1 vs 0.1 untreated catheter-associated urinary track infections/1000 bed-days) after 3 years when compared to those receiving copies of the guidelines only

Modified laboratory reports

- NCT02797613: Restricted Reporting for Positive Urine Cultures.
    - The study will compare traditional reporting of laboratory results with an alternative approach called restricted reporting. The microbiology laboratory will report "Positive urine cultures may represent asymptomatic bacteriuria or urinary tract infection. If urinary tract infection is suspected clinically, please call 777-xxxx (researcher mobile phone) for identification and susceptibility results." The primary outcome is proportion of asymptomatic bacteriuria treated with antibiotics within 7 days from positive culture. The adverse events of interest are pyelonephritis or sepsis measured 7 days from positive culture. The study was scheduled to begin recruitment in July 2016 and is scheduled for completion by December 2016.

Transplant recipients (6 studies)

- NCT02373085: Prospective Comparative Study about Treatment of Asymptomatic Bacteriuria in Kidney Transplant Recipients.

- The study compared antibiotics (adjusted to antibiogram) versus no treatment.
- The study had five primary outcomes: pyelonephritis, incidence of lower tract urinary infection; incidence of *Clostridium difficile* infection, incidence of multidrug resistant bacteria colonization/infection, and long-term graft function.
- A paper published in 2016 reported no difference in the incidence of pyelonephritis between treatment group versus control group: in the intention-to-treat (7.5% [4/53] versus 8.4% [5/59]; OR 0.88; 95% CI: 0.22-3.47) or per-protocol populations (3.8% [1/26] versus 8.0% [4/50]; OR: 0.46; 95% CI: 0.05-4.34). They found no differences in any of the secondary outcomes.[41]

- NCT01771432: Antibiotic Treatment Versus No Therapy in Kidney Transplant Recipients with Asymptomatic Bacteriuria
  - The study compared antibiotics versus no treatment.
  - The study had five primary outcomes: incidence of pyelonephritis, renal function, need for hospitalization, graft loss, and mortality.
  - The study is labeled as "recruiting," but has no updates since December 2015.

- NCT01871753: The Bacteriuria in Renal Transplantation (BiRT) Study: A Trial Comparing Antibiotics Versus no Treatment in the Prevention of Symptomatic Urinary Tract Infection in Kidney Transplant Recipients With Asymptomatic Bacteriuria
  - The study compares antibiotics versus no treatment.
  - The study has one primary outcome: cumulative incidence of a first episode of symptomatic urinary tract infection at 12 months
  - The anticipated end date is July 2018.

- NCT02575495: A Randomized Control Trial of Antibiotic Treatment Duration for Asymptomatic Bacteriuria After Kidney Transplantation
  - The study compared 7 versus 14 days of antibiotics.
  - The study has four primary outcomes: symptomatic urinary tract infection, sepsis, graft function, and mortality rate.
  - The study was last updated in March 2016 and has no publications.

- NCT01349738: Asymptomatic Bacteriuria & Risk of Urinary Tract Infection in Renal Transplants (ASB)
  - The study compared antibiotics versus no treatment.

- The primary outcomes of interest are prevalence of asymptomatic bacteriuria and risk of developing symptomatic urinary tract infections or renal allograft injury.
- The study was last updated in 2011 and no publications were identified.

- NCT02113774: The Impact of Antimicrobial Treatment for Asymptomatic Bacteriuria in Renal Transplant Patients
  - The study will compare antibiotics (according to in-vitro susceptibility) versus no treatment.
  - The study has two primary outcomes: development of symptomatic urinary tract infection, and 25% reduction in estimated glomerular filtration rate (eGFR).
  - The anticipated end date is April 2019.

<u>Hemodialysis</u>

- NCT01570556: Clinical Impact of Bacteriuria on Chronic Inflammation in Asymptomatic Hemodialysis Patients
  - The study will compare antibiotics (according to in-vitro susceptibility) versus no treatment.
  - The study has two primary outcomes: change in serum inflammatory markers (C-reactive protein, interleukin-6) and cardiovascular events.
  - The study was scheduled to end in 2013. No publications were identified.

<u>Intermittent catheterization</u>

- NCT01884467: Randomized Placebo-Controlled Trial of Gentamicin Bladder Instillation for the Prevention of Urinary Tract Infection in Adults at High Risk for Cystitis Due to Intermittent Catheterization
  - The study compared instilled gentamicin versus no treatment.
  - The primary outcomes included rates of symptomatic urinary tract infection and asymptomatic bacteriuria, and a comparison antibiotic resistance rates.
  - The study was scheduled to end in December 2015. No publications are available.

<u>Cardiac surgery</u>

- NCT01089712: Management Practices and the Risk of Infection Following Cardiac Surgery.
  - The purpose of the study is to determine the best ways to prevent infections after heart surgery
  - The primary endpoint will be major infection within 60 days of index cardiac surgical intervention

- As secondary outcomes, they will measure the incidence of other infections within 60 days of cardiac surgical intervention; superficial incisional surgical site infection; Symptomatic urinary tract infection or asymptomatic bacteriuria.
- The study was completed in 2014 and has two publications associated with it, where asymptomatic bacteriuria or UTIs are not reported. [42, 43]

Alternatives to antibiotics (4 studies)

- NCT00506025: Effectiveness of Cranberry Ingestion on Bacterial Adhesion: Adjunct to Pilot Study of Daily Ingestion of Cranberry Juice for the Prevention of Asymptomatic Bacteriuria in Pregnancy
  - The study compared twice daily cranberry ingestion versus once daily cranberry ingestion versus twice daily deactivated cranberry placebo and found no difference in antimicrobial activity in the urine.
  - The study was not published but the reports were available in ClinicalTrials.gov.

- NCT00093938: Cranberry for Prevention of Bacteriuria in Pregnancy
  - The study compared cranberries with an unmentioned comparator (likely placebo). The outcomes were asymptomatic bacteriuria and pre-term birth.
  - The study was last updated in 2010 and no publications are available.

- NCT01772875: Bladder Lavage as Decontamination Method for Asymptomatic Bacteriuria with Uropathogens in Catheterized Patients
  - The study was conducted at a specialized multiple sclerosis hospital in Belgium.
  - The study compared antiseptic bladder lavage versus pulsatile lavage with physiologic serum with outcomes of urinary culture and pyuria.
  - The study was scheduled to end in 2014. There are no publications.

- NCT00927316: *E. Coli* 83972 Induced Asymptomatic Bacteriuria (ABU) in Patients With Recurrent Urinary Tract Infections (urinary tract infection)
  - The study compared intravesical inoculation (by urethral catheterization) with 30 ml *E. coli* 83972 versus an identical procedure with saline with outcomes of urinary culture and pyuria.
  - The study was last updated in 2011 and no publications are available.

NIH Reporter results

We searched NIH Reporter on September 4, 2016 for "asymptomatic bacteriuria" and found 7 currently funded projects. These include a career-development award to study the transition from asymptomatic bacteriuria to urinary tract infection (5K99DK105205-02), a core grant to identify metabolomic biomarkers of high-risk bacteriuria in hospitalized patients (1U54CK000482-01), a randomized trial to test the dissemination of a toolkit to 40 nursing homes to improve prescribing of antibiotics in the setting of suspected urinary tract infections (5R18HS023779-02), and a study of catheter biofilms in asymptomatic bacteriuria compared with urinary tract infections (4R01GM103598-04). No study compared treatments for asymptomatic bacteriuria.

Projects funded by PCORI or the Agency for Healthcare Research and Quality

No funded studies were identified when we searched the Research & Results page on September 4, 2016.[44]

The Agency for Healthcare Research and Quality has funding in place for antimicrobial stewardship programs related to the President's National Strategy for Combating Antibiotic-Resistant Bacteria (CARB).[45] CARB also spurred an international program to fund alternatives to antibiotics in pre-clinical studies.[46] The CARB-X program is funded by international organizations including the National Institutes of Health and the Wellcome Trust (http://www.carb-x.org/partners).

8. Likelihood of Implementation of Research Results in Practice

Recommendations for specific antibiotics are likely to be used if provided on the laboratory report.

It is hard to predict how clinicians and their patients will respond to recommendations for watchful waiting, but patient-facing efforts to decrease unnecessary antibiotic use are becoming more common.[47] Such efforts may help to facilitate deferred treatment for asymptomatic bacteriuria if the recommendations are clear and supported by strong evidence with attention to potential legal implications.

The Veterans Affairs study (NCT01052545) that provided audit-feedback took several years to implement and included one-on-one feedback with personnel. It is possible for adherence to guidelines to change, but there should be realistic expectations regarding the amount of time and resources needed to influence behavior change.

9. Durability of Information

The results are likely to be durable. Antimicrobial resistance is a recognized problem in healthcare facilities and is expected by international economic groups to have an economic toll on society at large.[16, 17]

10. Potential Research Questions

Listed in order of relevance, with the first one being the most important.

What are the benefits and harms of using the Loeb criteria (or a similar algorithm) to create a treatment decision tool?

A study could compare the tool with the standard of care (*e.g.,* providing the comparison population with a copy of the IDSA guidelines) similar to the Veterans Affairs study. Priority outcomes of interest could include 1) Resolution of the symptoms that prompted treatment versus no treatment 2) Occurrence of an antibiotic-associated infection (*i.e., C. difficile);* 3) An assessment of patient and family satisfaction with the treatment plan**,** and 4) Mortality, hospitalizations and adverse outcomes.

Rationale for the research question: Genitourinary tract infections are a spectrum from asymptomatic bacteriuria through definite urinary tract infection to upper tract infections involving the kidney and bloodstream, like pyelonephritis and urosepsis. It can be difficult to identify those in the middle ground with possible symptoms or unclear symptoms due to other conditions. Those in the middle ground tend to be elderly, patients with multiple comorbidities or patients after transplantation. These populations have a week immune system and are at greatest risk of overprescription and overtreatment with antibiotics. Some harms are higher of *Clostridium difficile* colitis and multi-drug resistant infections and risks with undertreatment, making the decision to treat a higher stakes decision. The guidelines do not provide a clear "checklist" on when to treat these middle ground patients. The Loeb criteria are proposed to prioritize treatment with antibiotics for asymptomatic or possible bacteriuria. However, there is no landmark study that tests the benefits and harms of using this tool. Physicians are hesitant to use this tool without a landmark study.

What does watchful waiting entail?

A study could compare different methods of promoting communication between patients and clinicians about symptoms of urinary tract infections after the diagnosis of asymptomatic bacteriuria, or different methods of re-engaging with the healthcare system to investigate symptoms that may occur later. Patient and family satisfaction with this approach should be measured.

Rationale for the research question: While the guidelines and the most recent evidence show that asymptomatic bacteriuria should not be treated, clinicians need better information about what symptoms the patient should be advised to watch out for to prompt follow up with the provider when they occur. What steps can be taken in the office setting to make sure that the patient is able to access their healthcare provider rapidly when symptoms do occur? What information do patients feel they need to have to make the best decision for themselves?

What are the outcomes of screening and treatment prior to urologic procedures versus no screening?

Rationale for the research question: The recommendations are inconsistent across organizations. The IDSA recommends screening and treatment for asymptomatic bacteriuria prior to urologic procedures with anticipated mucosal bleeding, ACOG recommends screening prior to all urogynecologic procedures, but the USPSTF does not recommend screening prior to any urologic or urogynecologic procedure. High priority research could examine screening and treatment patterns for specific urologic procedures and the risk/benefit ratio of antibiotic treatment versus watchful waiting. For example, asymptomatic bacteriuria screening is recommended prior to urogynecologic and urologic procedures, but the adherence with this recommendation is not known. The adherence to screening prior to hysterectomy is hypothesized to be particularly low despite the high prevalence of peri-procedural urodynamics, cystoscopy and catheterization, and the high prevalence of hysterectomies among American women. Research is needed to improve understanding of the role that treatment for asymptomatic bacteriuria prior to the procedure may play in preventing post-procedural urinary tract infections.

Is there a need to rethink the use of broad spectrum versus targeted antibiotics or alternate treatments to treat asymptomatic bacteriuria?

A study could compare different antibiotics or antiseptics for treatment among those who are asymptomatic.

Rationale for the research question: Broad-spectrum antibiotics are the standard treatment.

What is the best way to communicate the decision to not treat asymptomatic bacteriuria to patients?

Rationale for the research question: Novel methods are needed to inform the risk-benefit analysis of treatment for asymptomatic conditions, such as asymptomatic bacteriuria, with antibiotics. The large burden of asymptomatic bacteriuria in certain high risk groups of adults (*i.e.,* those with diabetes or in long-term care facilities) and the variety of patients at increased

risk could make this an ideal population to test novel methods to quantify risk-benefit or communicate risk-benefit to providers and patients.

11. Conclusion

Screening and treatment for asymptomatic bacteriuria has both guideline established indications (*i.e.,* pregnancy) and controversies (*i.e.,* prior to urogynecologic procedures). The primary treatment is antibiotics which raises concerns for antibiotic resistance and the risk-benefit of antibiotics among individuals at-risk of antibiotic associated infections. A Veterans Affairs study that offered intensive audit-feedback was able to change practice patterns, however, this intensity of resource utilization may not be feasible in all settings. The inconsistent guidelines, implications for antibiotic resistance and ability to innovate on the dissemination strategy make this a potentially desirable area for future funding.

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