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Review of Evidence Paper Practice and Patient Outcome Improvements of Prescribing First-line Antibiotics for Acute Uncomplicated Cystitis

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Review of Evidence Paper

Practice and Patient Outcome Improvements of Prescribing First-line Antibiotics for

Acute Uncomplicated Cystitis

Submitted by Ira Amayun

Abstract

Background: In 2017, the Centers for Disease Control and Prevention reviewed and published guidelines for prescribing antibiotics. These guidelines emphasized treating acute uncomplicated cystitis (AUC) with nitrofurantoin (NTF), sulfamethoxazole-trimethoprim (SMX-TMP), or fosfomycin (FM) as appropriate first-line agents.

Objective: This paper aims to evaluate whether provider adherence to prescribing NTF, SMX-TMP, or FM has improved since the 2017 CDC guidelines were released. The paper also examines patient outcomes in the treatment of AUC in non-pregnant women relative to use of prescribing guidelines.

Methods: A literature review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The Cochrane Risk of Bias Tool (2020) was used to assess publication bias. The John Hopkins Research Evidence Appraisal Tool (John Hopkins, 2017) was used to grade the articles. The design, study sample, and major findings of each article were identified for their utility in the review of evidence. The outcome measurements were as follows: adherence to appropriate prescription of first-line antibiotics for the treatment of AUC, improvement or complete resolution of symptoms, bacterial eradication, and cost-effectiveness.

Results: The literature searches in the PubMed and Cochrane databases resulted in 56 published studies. The initial review excluded 19 duplicates and 18 other publications that examined complicated urinary tract infection and pregnant women. Subsequent reviews further excluded 8

publications that were ineligible to meet the objective. After application of exclusion criteria, 11 peer-reviewed articles were ultimately included in this review.

Limitations: Publications were still limited since the CDC released a review of the IDSA 2011 UAC treatment guidelines in 2017. Although published in or after 2017, four of the studies included in this paper were retrospective, measuring data from prior to 2017. The studies reviewed in this paper assessed bacterial and symptom resolution between 9 and 28 days post-treatment at the most.

Conclusion: The review showed prescribers' increasing awareness of and efforts to adhering to antibiotic prescription guidelines in the treatment of AUC, such as the 2011 IDSA guidelines that were reviewed and published by the CDC in 2017. With the increasing pattern of adherence, the trials, systematic reviews, and meta-analyses included in this study presented strong evidence that first-line antibiotics FM, NTF, and SMX-TMP are equally efficacious and cost-effective in the treatment of AUC in non-pregnant women without concern for antibiotic resistance.

Keywords: Acute uncomplicated cystitis; first-line antibiotics; prescribing guidelines; prescribing adherence.

Introduction

About half of women report symptoms of urinary tract infection (UTI), and one-third require antibiotic treatment before they reach the age of 25. UTIs are responsible for a yearly occurrence of eight million clinic visits and hospitalizations and an overall annual cost of \$2.4 billion in the United States (Barber, Norton, Spivak, & Mulvey, 2013). However, the unnecessary use of antibiotics accounts for the increasing national and global prevalence of antibiotic resistance. Therefore, practice guidelines and research have aimed to reduce antibiotic use while effectively treating infections, such as UTIs in women.

In 2017, the Centers for Disease Control (CDC) reviewed and published guidelines for prescribing antibiotics. These guidelines emphasized treating acute uncomplicated cystitis (AUC) with nitrofurantoin (NTF), sulfamethoxazole-trimethoprim (SMX-TMP; for which local resistance is < 20%), or fosfomycin (FM) as appropriate first-line agents. AUC, or acute uncomplicated UTI (uUTI), is usually caused by *E. coli*. Symptoms include dysuria, frequent voiding of small volumes, and urinary urgency, while nitrites and leukocyte esterase in urinalysis are the most accurate indicators of AUC (CDC, 2017). This paper aims to evaluate whether provider adherence to prescribing NTF, SMX-TMP, or FM has improved since the 2017 CDC guidelines were released, and evaluate patient outcomes in the treatment of AUC in women relative to the prescription adherence.

Methods

Search Strategy

A literature review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), and a systematic search for articles was conducted in the PubMed and Cochrane search engines using Boolean operators (AND, OR).

The inclusion criteria included a publication year between 2017 and 2020, text in the English language, and articles that were peer-reviewed. The search terms “first-line antibiotics AND acute uncomplicated cystitis OR uncomplicated urinary tract infection” and “prescription adherence AND first-line antibiotics AND acute uncomplicated cystitis OR uncomplicated urinary tract infection” were initially used. The search terms were then modified to “outcomes AND first-line antibiotics AND acute uncomplicated cystitis OR uncomplicated urinary tract infection.” The search terms resulted in 15 publications from 2017–2020 from both the PubMed and Cochrane databases. Additional search terms were “nitrofurantoin AND cystitis,” “fosfomycin AND cystitis,” and “sulfamethoxazole-trimethoprim AND cystitis.”

Data Items

Prescriber adherence was measured based on the practitioner’s decision to treat AUC with the first-line antibiotics FM, SMX-TMP, or NTF in accordance with the Infectious Disease Society of America (IDSA) 2011 guidelines that were reviewed and publicized by the CDC in 2017. AUC patient outcomes were measured with improved or complete resolution of symptoms and/or microbiological response 28 days post-treatment at the most. Classic symptoms of AUC include dysuria, frequent voiding of small volumes, and urinary urgency, while nitrites and leukocyte esterase are the most accurate indicators in urinalysis. Microbiological response is defined as reduced bacterial pathogens in a quantitative urine culture at the test of cure visit post-treatment.

Risk of Bias

The Cochrane Risk of Bias Tool (2020) was used to assess publication bias (Table 3). Of the 11 publications, nine had a low risk of bias, while three of the nine had some concerns with randomization. One of the publications had some concerning risk for bias due to lack of

identification and measurement of comparable antibiotics. The quasi-experimental study had some concerning risk for bias because of possible overlapping interventions.

Summary Measurements

The primary outcome measurement was adherence to appropriate prescription of first-line antibiotics for the treatment of AUC, as opposed to prescription of fluoroquinolones (FQ) and β lactams. Clinicians did not meet adherence if a first-line antibiotic was not prescribed in the absence of contraindication showing that the patient did not meet the criteria for first-line antibiotic treatment. The secondary outcome measurement was the patients' outcome as a result of prescribing first-line antibiotics, whether improvement or complete resolution of symptoms and bacterial eradication in urinalysis. Cost-effectiveness was also an outcome measurement that included monetary factors and/or quality-adjusted life-months (QALMs).

Critical Appraisal Tool

The John Hopkins Research Evidence Appraisal Tool (John Hopkins, 2017) was used to grade the articles (Table 1). High-quality, good-quality, and low-quality ratings were used. Studies with consistent results, a sufficient sample size, a definitive conclusion, and consistent recommendations with thorough references to scientific evidence were graded as having high quality. Studies with reasonably consistent results, a sufficient sample size, an acceptably definitive conclusion, and reasonably consistent recommendations with some references to scientific proof were graded as having good quality. Studies with limited evidence, inconsistent results, a small sample size, and a vague conclusion were graded as having low quality. Table 2 provides a synthesis of each publication. The design, study sample, and major findings of each article were identified for their utility in the review of evidence.

Results

The literature searches in the PubMed and Cochrane databases resulted in 56 published studies (Diagram 1). After initial review, 19 duplicates were excluded. Additionally, 18 other publications were excluded, most of which included information on complicated UTI and pregnant women. Subsequent reviews further excluded 8 publications that were ineligible to meet the objective. After exclusions and inclusion, 11 peer-reviewed articles were included in the review: 10 quantitative studies and one qualitative study. Of these, one trial (Huttner et al., 2018), two systematic reviews and meta-analyses (Mitrani-Gold, Raychaudhuri, & Rao, 2020; Cai et al., 2020), and one retrospective study (Pedela et al., 2017) assessed bacterial eradication and clinical symptoms treatment with NTF, FM, SMX-TMP, FQ, and β lactams. Two meta-analyses (Sadler et al., 2017; Perrault, Dahan, Iliza, LeLorier, & Zhanel, 2017) and one prospective study (Sanyal, Husereau, Beahm, Smyth, & Tsuyuki, 2019) assessed the cost-effectiveness of treating AUC with SMX-TMP, NTF, FM, and pivmecillinam. Finally, one trial (Robinson, Barsoumian, Aden, & Giancola, 2019), two retrospective studies (Pedela et al., 2017; Yu, McKenna, Dumyati, Lubowski, & Carreno, 2020), one quasi-experimental study (Giancola et al., 2019), and one semi-structured interview (Grigoryan et al., 2019) assessed clinicians' adherence to prescribing first-line antibiotics (NTF, FM, SMX-TMP) to treat AUC.

Prescriber Adherence

Robinson et al. (2019) evaluated the appropriateness of empiric FQ use compared to NTF use for treating AUC and determined trends and predictors for the use of FQ. Women aged 19–64 who were given NTF, ciprofloxacin, or levofloxacin for AUC at five family medicine clinics were included in the study. Data concerning symptoms, comorbidities, allergies, creatinine clearance, recent antibiotic use, and urine culture were used to determine if empiric antibiotic

treatment was appropriate based on national guidelines and local susceptibility data. Of the 567 women included in the study, 395 were given NTF and 172 were given FQ. Of these, 343 (86.8%) and 18 (10.5%) were appropriately prescribed NTF and FQ, respectively. For women inappropriately prescribed FQ, 15 (87.8%) lacked contraindication to NTF. Therefore, the study suggested the need for additional intervention and education to improve and decrease use of FQ.

Yu et al. (2020) aimed to track and report outpatient antibiotic prescriptions in Medicare Part B older adult enrollees diagnosed with cystitis in an outpatient setting between 2016 and 2017 in New York state (NYS). Inclusion criteria included oral antibiotic prescription less than three days after diagnosis of cystitis in Part D claims. According to the retrospective cohort study, 50,658 prescriptions were written upon discharge diagnosis of cystitis in NYS from 2016–2017. First-line antibiotic prescriptions of NTF, SMX-TMP, and FM as well as β lactamase prescriptions increased, and FQ use decreased in both older female and male adults. The study suggested that the widespread prevalence of FQ and β lactamase prescriptions requires outpatient antimicrobial stewardship.

Giancola et al. (2019) conducted a quasi-experimental study that included women aged 18–64 years who were prescribed NTF, SMX-TMP, or ciprofloxacin within seven days of encounter at five family medicine clinics. Adherence to duration of treatment (DOT) based on IDSA (2011) guidelines was evaluated. Stewardship intervention included revising/adding default prescription instructions to targeted antimicrobials in an electronic health record (EHR) and a one-day in-service at two (intervention group) of the five clinics. A total of 787 pre-intervention patients were compared with 862 post-intervention patients. After intervention, the adherence rate to the recommended DOT increased from 31% to 89% for NTF and from 22% to 60% for SMX-TMP. Additionally, adherence to recommended DOT increased in clinics that

received education (33.7% vs. 90.2%; $p < 0.01$); these clinics increased adherence from 22.1% to 58.8% ($p < 0.01$). Revising or adding default prescription instructions and their DOT to targeted antimicrobials in an EHR and providing clinician in-service also increased adherence to first-line antibiotic DOT guidelines.

Pedela et al. (2017) evaluated changes in outpatient FQ and NTF use and resistance among *E. coli* isolates after a change in institutional guidance to use NTF over FQs for AUC. The study compared the period from January 2003 to June 2007, when FQs were recommended as a first-line therapy for acute uUTIs, with the period from July 2007 to December 2012, when NTF was recommended as the first-line therapy. The retrospective time series study included 5,714 adults treated for AUC and 11,367 outpatient *E. coli* isolates. After the change in institutional guidelines, FQ use showed an immediate 26% reduction, and FQ-resistant *E. coli* were stabilized. The use of NTF increased without changing NTF resistance.

Grigoryan et al. (2019) sought to understand why primary care providers (PCPs) choose certain antibiotics or durations of treatment and to identify the sources of information guiding antibiotic prescription decisions. The study conducted a semi-structured interview with 18 PCPs in two family medicine clinics in Texas. Most PCPs reported that they prescribed SMX-TMP or NTF, but sometimes for a longer duration than recommended by the IDSA (2011). The PCPs also described multiple considerations when prescribing antibiotics, including allergies, sex, pregnancy, older age, past antibiotic experience and susceptibilities, familiarity with the antibiotic, shorter treatment duration and better compliance, UTI frequency, diabetes, and cost. Many PCPs mentioned that NTF was not as “strong” or as “quick” as SMX-TMP, and most were unfamiliar with FM. Few PCPs relied directly on guidelines to treat uUTIs; only two recalled and

mentioned the IDSA (2011) guidelines. Additionally, the PCPs had widely differing opinions on the extent to which antibiotic resistance was a problem in their practice.

Bacterial Eradication and Symptoms Resolution

A retrospective pre/post-intervention study by Pedela et al. (2017) concluded that, with the immediate 26% reduction in FQ use from July 2007 to December 2012, FQ-resistant *E. coli* stabilized. Additionally, the non-significant increase in NTF use did not change the pattern of NTF-resistant *E. coli*. The use of oral cephalosporin, which is not a first-line antibiotic for AUC, also increased during the post-intervention period.

Huttner et al. (2018) compared the clinical and microbiological efficacy of NTF and FM for treating AUC in women. Their multinational, open-label, analyst-blinded, randomized clinical trial examined 513 women aged 18 years and older with symptoms of AUC. The participants were recruited at hospital and outpatient units in Geneva, Switzerland, from October 2013 to April 2017. Of the participants, 255 were randomized to take oral NTF in doses of 100 mg three times daily for five days, while 258 were randomized to take FM in a single 3-g dose. Of these participants, 475 (93%) completed the trial and returned 14 and 28 days after therapy. At 28 days, 171 of 244 (70%) of the NTF group and 139 of 241 (58%) of the FM group achieved clinical resolution. Microbiologic resolution occurred in 129 of 175 (74%) and 103 of 163 (63%) in the NTF and FM groups, respectively. The study concluded that the five-day NTF treatment had significantly higher clinical and microbiological resolution than single-dose FM treatment, with a few adverse gastrointestinal events of nausea and vomiting for both groups. The study did not refer to local antibiotic resistance data and did not include information on treatment with SMX-TMP.

Cai et al. (2020) performed a systematic review and meta-analysis to compare the effectiveness and safety profile, or adverse effects, of FM to those of SMX-TMP, NTF, FQ, and β lactams in women with AUC. The study included 15 random controlled trials (RCTs) and 2,295 adults. Of the studies, 14 that examined a total of 2,052 patients found no difference for microbial eradication (OR 1.03, 95% CI 0.83–1.30, $p = 0.09$). No difference for safety outcomes was found in 11 RCTs with a total of 1,816 patients (OR 1.17, 95% CI 0.86–1.58, $p = 0.33$). FM was associated with high patient compliance and was as effective and safe as SMX-TMP, NTF, FQ, and β lactams in the treatment of AUC. The study did not mention local antibiotic resistance.

Mitrani-Gold et al. (2020) conducted a systemic literature review and meta-analysis to estimate the treatment effect of NTF. Their analysis included 12 studies, including 11 trials. The study estimated the microbiological response rate for NTF and placebo treatments through cross-trial comparison and interstudy. Heterogeneity was assessed using Cochran's chi-square test. Microbiological response was defined as the reduction of bacterial pathogens to 10^3 CFU/ml (or no growth) in the microbial intent-to-treat population on a quantitative urine culture at the test of cure visit, five to nine days post-treatment. The overall microbiological response, with 95% confidence interval, was 0.766 (0.665, 0.867) for NTF and 0.342 (0.288, 0.397) for the placebo. Therefore, NTF was effective in the treatment of uUTIs with a conservative non-inferiority margin of 12.5%, which was consistent with the April 2018 FDA guidance that showed a non-inferiority margin of 10% (U.S. Food and Drug Administration, 2019). The study did not assess SMX-TMP and FM for their microbiological response rate.

Cost-effectiveness

Perrault et al. (2017) performed cost-minimization analysis using a decision tree model to compare the cost of treatment per patient in Ontario, Canada. As an option for first-line

empirical treatment of uUTIs, the cost of FM was compared with the current cost of treatment with sulfonamides, FQ, and NTF. All four antibiotics were found to be equally cost-effective.

Sadler et al. (2017) assessed the relative cost-effectiveness of SMX-TMP, FM, NTF, and pivmecillinam, which are currently recommended in England for treatment of uUTIs in adult women. Cost-effectiveness was assessed as cost per resolved UTI. The study aimed to guide clinicians in their empirical prescribing choice based on cost-effectiveness and local resistance levels. Actual prescribing practices varied between local areas. NTF was prescribed more than 2.3 million times in 2015. Prescribing SMX-TMP was still common despite evidence of high local resistance. The following treatments were the most effective for resolution (approx. 850 cases resolved per 1000) and had the lowest total cost: trimethoprim given in a 200-mg dose twice daily for seven days, FM given in a single 3-g dose, and NTF given in a 100-mg dose twice daily for seven days. Trimethoprim was estimated to be the most cost-effective treatment when resistance was $< 30\%$. If resistance to trimethoprim was $> 30\%$, then FM and NTF were the most cost-effective. These three antibiotics had the lowest total cost.

Sanyal et al. (2019) calculated the costs of antibiotic treatment and health services based on cost data from Canada. A probabilistic analysis was used to evaluate the impact of treatment strategies on costs and QALMs. Management of uUTIs by community pharmacists in Canada resulted in high cure rates and a high degree of patient satisfaction. Using prescribing guidelines, community pharmacists in New Brunswick, Canada, prescribed NTF, SMX-TMP, and FM in 88%, 8%, and 2% of cases, respectively, while physicians prescribed NTF, SMX-TMP, and FM in 55%, 26%, and 2% of cases, respectively. All patients were assumed to achieve resolution of symptoms in one month, including those who received a second round of treatment. The mean costs of community pharmacist, family physician, and emergency physician-initiated

management were \$72.47, \$141.53, and \$368.16, respectively. The mean QALMs of pharmacist, family physician, and emergency physician-initiated management were 0.75137, 0.75142, and 0.75146, respectively. Therefore, the community pharmacist-initiated and guided management was less costly and provided comparable QALMs compared to that initiated by family and emergency physicians when prescribing NTF, SMX-TMP, or FM to treat uUTIs.

Discussion

Summary of Evidence

All 11 studies, which included trials, systemic reviews and meta-analyses, retrospective studies, a quasi-experimental study, and a semi-structured interview study, were high quality and presented strong evidence of their findings. The 10 quantitative studies used robust statistical analysis to measure outcomes. Sadler et al. (2017) and Perrault et al. (2017) assessed cost-effectiveness with reference to local antibiotic resistance levels. Robinson et al. (2019), Giancola et al. (2019), and Pedela et al. (2017) assessed prescription adherence with reference to local antibiotic resistance. Giancola et al. (2019) assessed prescriber adherence with reference to IDSA (2011) guidelines for DOT and local antibiotic resistance. No bias secondary to funding was found.

The two systematic reviews and meta-analyses, one trial, and one retrospective study (Mitrani-Gold et al., 2020; Cai et al., 2020; Huttner et al., 2018; Pedela et al., 2017) concluded that FM, SMX-TMP, and NTF were equally effective for microbiological and symptom resolution of AUC 9–28 days after treatment. Fosfomycin trometamol was associated with high patient compliance. Trimethoprim, FM, and NTF had the lowest total cost. SMX-TMP was estimated to be the most cost-effective treatment when local resistance was < 30%. If resistance to SMX-TMP was > 30%, a single 3-g dose of FM or a twice-daily, 100-mg dose of NTF for

seven days was the most cost-effective treatment. The uUTI management guided by community pharmacists in Canada yielded high cure rates, lower costs, and comparable QALMs compared to management guided by family and emergency physicians when prescribing NTF, SMX-TMP, or FM (Sanyal et al., 2019).

Of the 11 publications, five showed that the lack of institutional guidelines yielded poor adherence in prescribing first-line antibiotics to treat AUC. The qualitative study suggested that few providers relied on the IDSA (2011) guidelines to treat uUTIs, and most providers described multiple factors in their decision-making when prescribing antibiotics, such as age, past antibiotic experience, shorter treatment, and familiarity with antibiotics. The FQ versus NTF study by Pedela et al. (2017) stated that the 87.8% women inappropriately prescribed FQ had a lack of contraindication to NTF. According to Giancola et al. (2019), revising or adding EHR default prescription instructions and their DOT, as well as clinician in-service, increased adherence to first-line antibiotic prescriptions. The study by Yu et al. (2020) tracked NYS adherence to CDC guidelines concerning the use of first-line antibiotics. Although the study reported increased prescriptions of first-line antibiotics and β lactams and decreased use of FQ, the study did not mention whether prescribers used institutional guidelines to determine their choice of antibiotics.

Limitations

This paper included peer-reviewed studies from 2017 to February 2020, but publications are still limited since the CDC released its review of the IDSA 2011 AUC treatment guidelines. Additionally, although published in or after 2017, four of the studies included in this paper were retrospective, measuring data from prior to 2017. Finally, the studies reviewed in this paper assessed bacterial and symptom resolutions at 9–28 days post-treatment at the most.

Conclusion

Since the 2017 CDC AUC treatment guidelines were released, there have not been enough studies to assess increased prescriber adherence to using first-line antibiotic in the treatment of AUC. Out of the 11 studies included in this paper, 10 showed the prescribers' increasing awareness of and efforts to adhere to antibiotic prescription guidelines, such as the 2011 IDSA guidelines that were reviewed and published by the CDC in 2017. With the increasing pattern of adherence, the trials, systematic reviews, and meta-analyses in this study presented strong evidence that first-line antibiotics FM, NTF, and SMX-TMP are equally cost-effective and efficacious in the treatment of AUC in non-pregnant women, without concern for antibiotic resistance. Studies who referenced to prescription guidelines in the use of first-line antibiotics and local antibiotic resistance yielded desired patient outcomes in terms of bacterial and symptom resolution and cost-effectiveness.

Institutional AUC treatment management guidelines embedded in EHR could increase prescriber adherence to using first-line antibiotics. Institutional management guidelines should include FM, NTF, and SMX-TMP as first-line antibiotics, as well as local antibiotic susceptibility or antibiograms and DOTs in the presence of other deciding factors, such as comorbidities and older age. Clinicians should also be informed of positive patient outcomes as a result of their adhering to appropriate antibiotic prescription practices. This paper suggests further studies to quantify prescriber adherence to the 2011 IDSA and 2017 CDC guidelines.

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Appendix

Diagram 1

Reviews based on Prisma diagram



PRISMA 2009 Flow Diagram©

Criteria: Literature in English, published between 2017-February 21, 2020, meeting medical search terms.

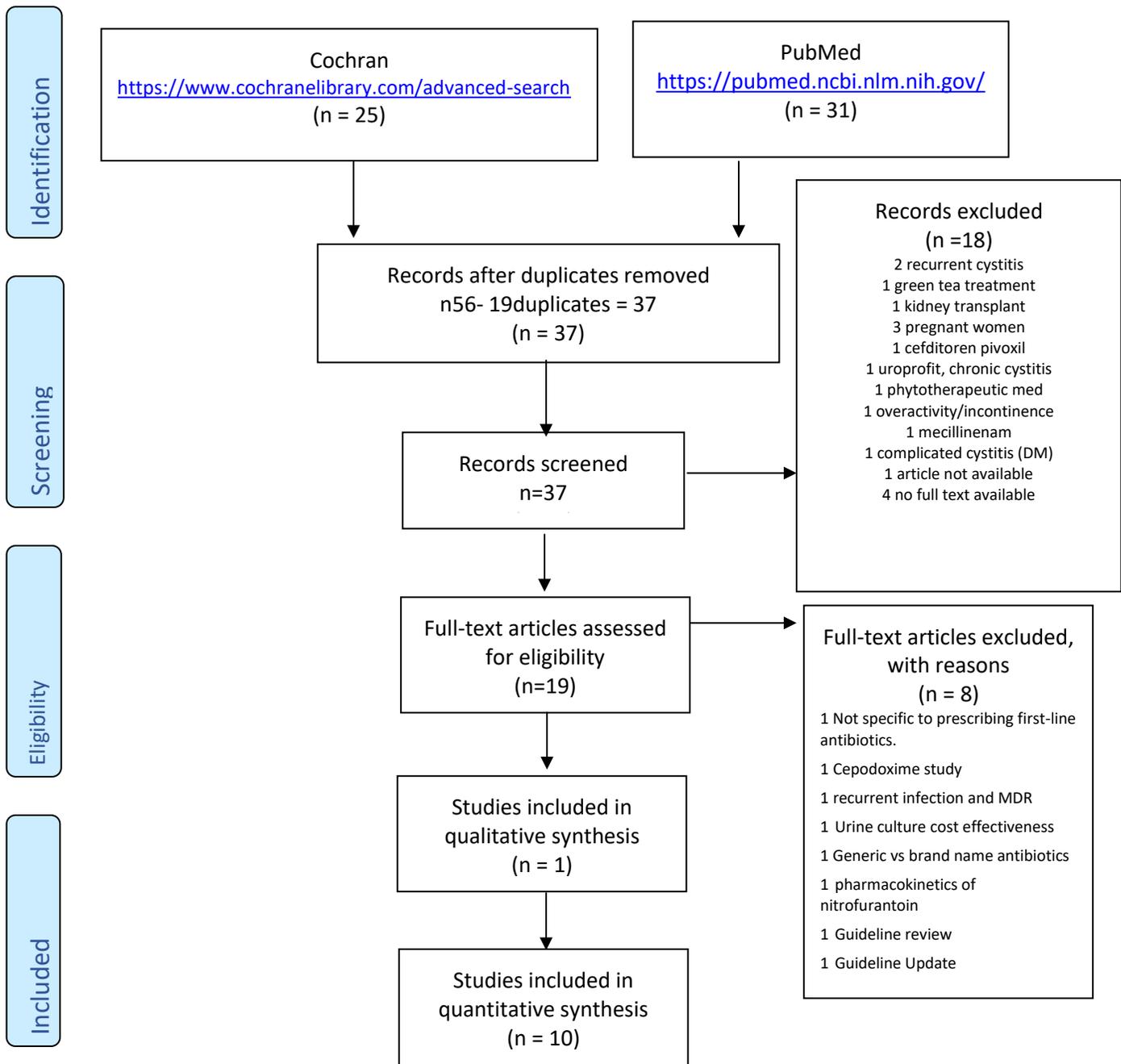


Table 1

Evaluation Table for Critical Appraisal

Citation	Conceptual Framework	Design/Method	Sampling/Setting	Major variables studied and their definitions	Measurement of Major Variables	Data Analysis	Major Findings	Appraisal of Worth to Practice
Cost-Effectiveness Analysis of Fosfomycin for Treatment of Uncomplicated Urinary Tract Infections in Ontario. Perrault L, et al. (2017)	Decision-Tree Model (Tree Age Pro 2015 software)	Cost-minimization analysis, meta-analysis	Data were obtained from Physician Services (2016), Ontario Case Costing Initiative, and Pharma Stat provincial data.	Costs-province-level data on drug cost Probabilities-probabilities of resistance, effectiveness	Cost was computed based on prices in the Ontario Drug Benefit Formulary and the recommended dosage for uUTIs. Probabilities for effectiveness were assumed to be equal for all antibiotics based on meta-analysis by Falagas et al. (2010).	Cost-minimization analysis, meta-analysis Resistance rates for fosfomycin were obtained from Antimicrobial Resistance Epidemiological Survey on Cystitis.	The analysis revealed that the cost per patient for uncomplicated UTI treatment is similar for all 4 antibiotics, from \$96.19 for sulfonamides to \$105.12 for fosfomycin. Fosfomycin has lower resistance profile, safe, effective and offers a single dose regimen for treatment of uUTI and is associated with high degree of compliance.	Good
Cost-effectiveness of antibiotic treatment of uncomplicated urinary tract infection in women: a comparison of four antibiotics. Sadler S, et al. (2017)	Decision tree economic model updated to include UK-specific costs.	Systems review, network meta-analysis Probabilistic economic and deterministic sensitivity analyses.	The systematic review identified 11 studies that formed a connected evidence network meta-analysis.	Clinical effectiveness-clinical cure rates in 16 days, including two treatment courses. Cost effectiveness was assessed as cost per UTI resolved, and based on local resistance level The outcome was cost per UTI resolved	Clinical cure rates were informed by a systemic review and network meta-analysis.	Trimethoprim 200 mg twice daily for 3 or 7days was estimated to be the most cost-effective treatment when resistance was <30%. If resistance to trimethoprim was > 30%, fosfomycin 3g once and nitrofurantoin 100 mg twice daily for 7days were most cost-effective.	Based on recent estimates of trimethoprim resistance rates in England, a single 3 g dose of Fosfomycin is likely the most cost-effective treatment option for uncomplicated UTIs in women.	High
Cost-effectiveness and budget impact of the management of uncomplicated urinary tract infection by	A decision analytic model was used to compare costs and outcome of community	Prospective Study of community pharmacists in New Brunswick, Canada between	Cure rates and utilities were derived from published studies. Cost of antibiotic treatment and health services use were	Pharmacist services-pharmacists prescribing for women presenting with uncomplicated UTI	Cost-effectiveness Sensitivity to cure rates	Using prescribing guidelines, community pharmacist in New Brunswick, Canada	The community pharmacist-initiated and guided management was less costly and gave	High

community pharmacists. Sanyal et al. (2019)	pharmacist-initiated management of uncomplicated UTI to family or emergency physician-initiated management.	June 2017 and April 2018. Probabilistic analysis to evaluate impact of treatment strategies on cost and quality-adjusted-life-months (QALMS) Cost-utility analysis	calculated based on cost data from Canada. There was no population sampling mentioned in this study.	Pharmacist-initiated-community pharmacist assessed and prescribed antibiotics, following guidelines, to women presenting with uncomplicated UTI. Physician initiated-physician prescribed antibiotics to women presenting with uncomplicated UTI.	Societal perspective	prescribed more pharmacist prescribed 88%, 8% and 2% of Nitrofurantoin, TMP-SMX, and Fosfomycin respectively, while physicians prescribed 55%, 26%, and 2% of Nitrofurantoin, TMP-SMX, and Fosfomycin respectively. All patients were assumed to achieve resolution of symptoms in one month including those who received second round of treatment.	comparable QALMs compared to family and emergency physicians in prescribing Nitrofurantoin, TMP-SMX, or Fosfomycin for the treatment of uncomplicated UTIs.	
Qualitative Analysis of Primary Care Provider Prescribing Decisions for Urinary Tract Infections Grigoryan et al. (2019)	Mapping and sequencing behaviors, using the Cabana framework which includes knowledge, attitudes, and external factors.	Qualitative semi-structured interviews and thematic analysis	18 primary care providers practicing in two family medicine clinics in a large urban area in Texas, between July 2017 and November 2017.	Providers' knowledge, attitudes, and external factors	Thematic analysis identified seven themes related to providers' prescribing decisions for acute cystitis.	Most providers reported they would prescribe TMP-SMX or Nitrofurantoin but sometimes longer duration than recommended by the 2010 Infectious Disease Society of America (IDSA); providers described multiple consideration when prescribing antibiotics; many providers mentioned that Nitrofurantoin is not as "strong" and not as "quick"; most providers were unfamiliar with Fosfomycin; few providers directly relied on guidelines; only two providers recalled and mentioned the IDSA guidelines; providers had	Few providers relied on IDSA guideline in the treatment of uncomplicated UTIs.	Good

						widely differing opinions on the extent to which antibiotic resistance is a problem in their own practices		
Antibiotic Prescribing in New York State Medicare Part B Beneficiaries Diagnosed with Cystitis Between 2016 and 2017 Yu et al. (2020)	Geographical antimicrobial prescribing patterns	Retrospective, cohort study of Medicare Part B enrollees in New York State	There were 23,981 and 26,677 prescriptions written for cystitis across NYS in 2016 and 2017. Data were stratified by sex. Annual prescriptions proportions were compared using χ^2 test or Fisher's exact test.	IDSA guidelines: Nitrofurantoin, Trimethoprim-sulfamethoxazole, and fosfomycin were categorized as first-line agents. B-lactams and Fluoroquinolones are categorized as others.	Counts and proportion were used to describe the year-specific overall prescribing rate for each antibiotic category.	The χ^2 tests were used to assess changes in antibiotic prescribing pattern, adherence to IDSA guidelines and quinolone prescribing rates from 2016 to 2107. Heat maps were used to describe relative change between years for prescribing within specific regions.	First-line antibiotic with Nitrofurantoin, TMP-SMX, and Fosfomycin prescription and B lactamase prescriptions increased, and fluoroquinolone use decreased in both older female and male adults.	Good
Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: a Randomized Clinical Trial. Huttner et al. (2018)	Flow chart comparison of clinical and microbiological efficacy of Nitrofurantoin and Fosfomycin	Multinational, open-label, analyst-blinded, randomized clinical trial	513 non-pregnant women aged 18 years and older with symptoms of acute uncomplicated cystitis was conducted in Geneva, Switzerland from October 2013 to April 2017. Participants were recruited at hospital units and outpatient units.	Primary outcome-clinical resolution in the 28 days following therapy Failure- need for additional of change in antibiotic treatment due to UTI or lack of efficacy Secondary outcomes-bacteriostatic response and incidence of adverse events.	Statistical analysis with 95% confidence interval. Primary and secondary outcomes were calculated using χ^2 tests.	At 28 days, 171 of 244 (70%) of the Nitrofurantoin group and 139 of 241 (58%) achieved clinical resolution. Microbiologic resolution occurred in 129 of 175 (74%) and 103 of 163 (63%) in the Nitrofurantoin and Fosfomycin groups, respectively.	5-day Nitrofurantoin significantly has higher clinical and microbiological resolution than single-dose Fosfomycin, with few gastrointestinal adverse events of nausea and vomiting for both groups.	Good
Preferential Use of Nitrofurantoin Over Fluoroquinolones for Acute Uncomplicated Cystitis and Outpatient Escherichia coli Resistance in an Integrated Healthcare System. Pedela RL, et al. (2017)	Comparison of two time periods (by time series analysis)	Retrospective pre-intervention post-intervention study.	Urban setting in Colorado, 477-bed hospital, emergency department and urgent care department, eight community health clinics, and 15 school-based clinics. study included 5,714 adults treated for acute cystitis and 11,	Main outcomes-changes in Fluoroquinolones and Nitrofurantoin use and resistance among E. coli isolates. Secondary outcome-change in total outpatient use, appropriateness of	Manual review of medical records of 100 randomly selected patients prescribed Fluoroquinolones. Electronic laboratory data were expressed for E. coli isolates resistant to Fluoroquinolones or	Time series analysis. Jan 2003-Jan 2007 when Fluoroquinolones were recommended as first-line therapy for acute uncomplicated UTI and Jul 2007- Dec 2012 when Nitrofurantoin was recommended.	After a change in the institutional guidelines, there was an immediate 26% reduction in Fluoroquinolone use and stabilization in Fluoroquinolone resistant E. coli. There was an increased use of	High

			367 outpatient E. coli isolates.	fluoroquinolone prescription, and occurrence of UTI-related clinical events in the 28 days after the index visit.	Nitrofurantoin overtime.	Autoregressive integrated moving average, correlation, and Chi-square test were for analyses.	Nitrofurantoin use without a change in nitrofurantoin resistance.	
Evaluation of the trends and appropriateness of fluoroquinolone use in the outpatient treatment of acute uncomplicated cystitis at five family practice clinics. Robinson, et al. (2019)		Retrospective Study	19-64 YO women seen at five family medicine clinics and prescribed nitrofurantoin, ciprofloxacin, or levofloxacin for uncomplicated cystitis	Appropriateness of Nitrofurantoin or Fluoroquinolone treatment.	Comorbidities, allergies, creatinine clearance, recent antibiotic use and urine culture data were used to determine appropriate empiric antibiotic treatment. Descriptive statistic, Pearson's chi-square or Fisher's exact test, Student's t-test, and multivariate logistic regression were used.	Of the 567 women included in the study, 395 were given Nitrofurantoin and 172 were given Fluoroquinolones. 343 or 86.8% and 18 or 10.5% were appropriately prescribed Nitrofurantoin and fluoroquinolones, respectively. For women inappropriately Fluoroquinolones, 15 or 87.8% lack contraindication to Nitrofurantoin.	The study suggests the need for additional intervention and education to improve and decrease use of Fluoroquinolones	High
Fosfomycin Trometamol versus Comparator Antibiotics for the Treatment of Acute Uncomplicated Urinary Tract Infections in Women: A Systematic Review and Meta-Analysis. Cai T et al. (2020)		Systematic Review and meta-analysis	15 RCTs were included, with a total of 2,295 female patients older than 18 years old	Microbial cure-eradication of infecting strain with no recurrent bacteriuria. Clinical cure-complete resolution of symptoms at the end of treatment Safety outcomes-presence or absence of adverse effects	95% CI, crude ORs and log ORs was calculated to analyze dichotomous data. Forest plot diagrams, funnel plot, and chi-square were used for sample sizes and variations among studies.	The study included 15 RCT which found no difference for microbial eradication 14 RCT with total of 2,052 patients (OR 1.03, 95% CI 0.83-1.30, p=.09). No difference for safety outcome in 11 RCT in a total of 1,816 patients (OR 1.17, 95% CI 0.86-1.58, p=0.33).	Fosfomycin trometamol is associated with high patient compliance and is as effective and safe in comparison to comparator antibiotic in the treatment of acute uncomplicated cystitis.	High
Improvement in adherence to antibiotic duration of therapy recommendations for uncomplicated cystitis: a quasi-experimental study.		Quasi-experimental study	Women aged 18-64 years who were prescribed Nitrofurantoin, TMX-SMT, or ciprofloxacin within seven days of encounter at five family medicine clinics.	A stewardship intervention consisting of revising/adding default prescribing instructions to targeted antimicrobials in an HER. One day in-	Pre and post intervention periods were assessed. Chi-square or Fisher's exact test, and Cochran Armitage Trend test were used to analyze	A total of 787 patients in the pre-intervention and 862 patients in post intervention were compared. After intervention, the adherence rate to the	Clinics which received education increased adherence from 22.1% to 58.8%; $P<0.01$. Revising/adding default prescribing	High

<p>Giancola SE, et al. (2019)</p>				<p>service/ education was part of the interventions.</p> <p>Duration of treatment (DOT)- 5 days for Nitrofurantoin, 3 days for TMX-SMT, fosfomycin 1 dose, and 3 days for Ciprofloxacin.</p>	<p>nominal data. Student's t-test was used to analyzed continuous data. Two tailed P-values ≤ 0.05 were considered significant.</p>	<p>recommended DOT for Nitrofurantoin increased from 31% to 89% and an increased from 22% to 60% for TMX-SMT. Adherence to recommended DOT increased in clinics which received education (33.7% vs 90.2%; $P < 0.01$). Clinics which did not received education increased adherence from 22.1% to 58.8%; $P < 0.01$.</p>	<p>instructions to targeted antimicrobials and their DOT in an EHR, and in-service, increased clinician adherence to uncomplicated cystitis first-line antibiotic DOT guidelines.</p>	
<p>Systematic Review and Meta-analysis to Estimate the Antibacterial Treatment Effect of Nitrofurantoin for a Non-Inferiority Trial in Uncomplicated Urinary Tract Infection. Mitrani-Gold FS, et al. (2020)</p>		<p>Systemic literature review and meta-analysis</p>	<p>Search resulted in a total of 2048 publications. Of these 76 met eligibility criteria. After inclusion and exclusion, twelve studies, including 11 trials were included in meta-analysis.</p>	<p>Microbiological response- AS per FDA guidance, defined as reduction of bacterial uropathogen recovered at study entry to $< 10^3$ or at by at least 1-log decrease (CFU/ml) on quantitative urine culture at the test-of-cure-visit.</p>	<p>The study estimated the microbiological response rate for nitrofurantoin and placebo through cross trial comparison and inter-study heterogeneity was assessed with Cochran's chi-square test. The overall microbiological response rate along with 95% confidence interval were presented in forest plots.</p>	<p>The overall microbiological response (95% confidence interval) was 0.766 (0.665, 0.867) for nitrofurantoin and 0.342 (0.288, 0.397) for placebo.</p>	<p>The corresponding treatment effect estimate for Nitrofurantoin supports the conservative non-inferiority margin of 12.5% and is consistent with the recently published FDA guidance.</p>	<p>High</p>

Table 2

Evidence Synthesis Table

Studies	Design	Sample	Outcome/Findings
Cost-Effectiveness Analysis of Fosfomycin for Treatment of Uncomplicated Urinary Tract Infections in Ontario. Perrault L, et al. (2017)	Cost-minimization analysis, meta-analysis	Data were obtained from Physician Services (2016), Ontario Case Costing Initiative, and Pharma Stat provincial data.	The analysis revealed that the cost per patient for uncomplicated UTI treatment is similar for all 4 antibiotics, from \$96.19 for sulfonamides to \$105.12 for fosfomycin. Fosfomycin has lower resistance profile, safe, effective and offers a single dose regimen for treatment of uUTI, associated with high degree of compliance.
Cost-effectiveness of antibiotic treatment of uncomplicated urinary tract infection in women: a comparison of four antibiotics. Sadler S, et al. (2017)	Systems review, network meta-analysis Probabilistic economic and deterministic sensitivity analyses.	The systemic review identified 11 studies that formed a connected evidence network meta-analysis.	Based on recent estimates of trimethoprim resistance rates in England, a single 3 g dose of Fosfomycin is likely the most cost-effective treatment option for uncomplicated UTIs in women.
Cost-effectiveness and budget impact of the management of uncomplicated urinary tract infection by community pharmacists. Sanyal et al. (2019)	Prospective Study of community pharmacists in New Brunswick between June 2017 and April 2018. Probabilistic analysis to evaluate impact of treatment strategies on cost and quality-adjusted-life-months (QALMS) Cost-utility analysis	The systemic review identified 11 studies that formed a connected evidence network meta-analysis.	The community pharmacist-initiated and guided management was less costly and gave comparable QALMS compared to family and emergency physicians in prescribing Nitrofurantoin, TMP-SMX, or Fosfomycin for the treatment of uncomplicated UTIs.
Qualitative Analysis of Primary Care Provider Prescribing Decisions for Urinary Tract Infections Grigoryan et al. (2019)	Qualitative semi-structured interviews and thematic analysis.	18 primary care providers practicing in two family medicine clinics in a large urban area in Texas, between July 2017 and November 2017.	Few providers relied on IDSA guideline in the treatment of uncomplicated UTIs.
Antibiotic Prescribing in New York State Medicare Part B Beneficiaries Diagnosed with Cystitis Between 2016 and 2017 Yu et al. (2020)	Retrospective, cohort study of Medicare Part B enrollees in New York State.	There were 23,981 and 26,677 prescriptions written for cystitis across NYS in 2016 and 2017.	TMP-SMX, and Fosfomycin prescription and B lactamase prescriptions increased, and fluoroquinolone use decreased in both older female and male adults. The study suggests widespread prevalence of fluoroquinolone and B lactamase prescribing needs outpatient antimicrobial stewardship.
Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: a Randomized Clinical Trial Huttner et al. (2018)	Multinational, open-label, analyst-blinded, randomized clinical trial	513 non-pregnant women aged 18 years and older with symptoms of acute uncomplicated cystitis was conducted in Geneva, Switzerland from October 2013 to April 2017. Participants were	5-day Nitrofurantoin significantly has higher clinical and microbiological resolution than single-dose Fosfomycin, with few gastrointestinal adverse events of nausea and vomiting for both groups.

		recruited at hospital units and outpatient units.	
Preferential Use of Nitrofurantoin Over Fluoroquinolones for Acute Uncomplicated Cystitis and Outpatient Escherichia coli Resistance in an Integrated Healthcare System. Pedela RL, et al. (2017)	Retrospective pre-intervention post-intervention study.	Urban setting in Colorado, 477-bed hospital, emergency department and urgent care department, eight community health clinics, and 15 school-based clinics. study included 5,714 adults treated for acute cystitis and 11,367 outpatient E. coli isolates.	After a change in the institutional guidelines, there was an immediate 26% reduction in Fluoroquinolone use and stabilization in Fluoroquinolone resistant E. coli. There was an increased use of Nitrofurantoin use without a change in nitrofurantoin resistance.
Evaluation of the trends and appropriateness of fluoroquinolone use in the outpatient treatment of acute uncomplicated cystitis at five family practice clinics. Robinson, et al. (2019)	Retrospective Study	19-64 YO women seen at five family medicine clinics and prescribed nitrofurantoin, ciprofloxacin, or levofloxacin for uncomplicated cystitis	Of the 567 women included in the study, 395 were given Nitrofurantoin and 172 were given Fluoroquinolones. 343 or 86.8% and 18 or 10.5% were appropriately prescribed Nitrofurantoin and fluoroquinolones, respectively. For women inappropriately Fluoroquinolones, 15 or 87.8% lack contraindication to Nitrofurantoin.
Fosfomycin Trometamol versus Comparator Antibiotics for the Treatment of Acute Uncomplicated Urinary Tract Infections in Women: A Systematic Review and Meta-Analysis. Cai T et al. (2020)	Systematic Review and meta-analysis	15 RCTs were included, with a total of 2,295 female patients older than 18 years old	Fosfomycin trometamol is associated with high patient compliance and is as effective and safe in comparison to comparator antibiotic in the treatment of acute uncomplicated cystitis.
Improvement in adherence to antibiotic duration of therapy recommendations for uncomplicated cystitis: a quasi-experimental study. Giancola SE, et al. (2019)	Quasi-experimental study	Women aged 18-64 years who were prescribed Nitrofurantoin, TMX-SMT, or ciprofloxacin within seven days of encounter at five family medicine clinics.	Clinics which received education, with revised EHR, increased adherence from 22.1% to 58.8%; $P < 0.01$. Revising/adding default prescribing instructions to targeted antimicrobials and their DOT in an EHR, and in-service, increased clinician adherence to uncomplicated cystitis first-line antibiotic DOT guidelines.
Treatment Effect of Nitrofurantoin for a Non-Inferiority Trial in Uncomplicated Urinary Tract Infection. Mitrani-Gold FS, et al. (2020)	Systemic literature review and meta-analysis.	Search resulted in a total of 2048 publications. Of these 76 met eligibility criteria. After inclusion and exclusion, twelve studies, including 11 trials were included in meta-analysis.	The corresponding treatment effect estimate for Nitrofurantoin supports the conservative non-inferiority margin of 12.5% and is consistent with the recently published FDA guidance.

Table 3

Bias Assessment Using Cochrane Risk of Bias Tool

Study	D1	D2	D3	D4	D5	Overall
Cost-Effectiveness Analysis of Fosfomycin for Treatment of Uncomplicated Urinary Tract Infections in Ontario. Perrault L, et al. (2017)	●	●	●	●	●	●
Cost-effectiveness of antibiotic treatment of uncomplicated urinary tract infection in women: a comparison of four antibiotics. Sadler S, et al. (2017)	●	●	●	●	●	●
Cost-effectiveness and budget impact of the management of uncomplicated urinary tract infection by community pharmacists. Sanyal et al. (2019)	●	●	●	●	●	●
Qualitative Analysis of Primary Care Provider Prescribing Decisions for Urinary Tract Infections Grigoryan et al. (2019)	●	●	●	●	●	●
Antibiotic Prescribing in New York State Medicare Part B Beneficiaries Diagnosed with Cystitis Between 2016 and 2017	●	●	●	●	●	●
Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: a Randomized Clinical Trial. Huttner et al. (2018)	●	●	●	●	●	●
Preferential Use of Nitrofurantoin Over Fluoroquinolones for Acute Uncomplicated Cystitis and Outpatient Escherichia coli Resistance in an Integrated Healthcare System. Pedela RL, et al. (2017)	●	●	●	●	●	●
Evaluation of the trends and appropriateness of fluoroquinolone use in the outpatient treatment of acute uncomplicated cystitis at five family practice clinics. Robinson, et al. (2019)	●	●	●	●	●	●
Fosfomycin Trometamol versus Comparator Antibiotics for the Treatment of Acute Uncomplicated Urinary Tract Infections in Women: A Systematic Review and Meta-Analysis. Cai T et al. (2020)	●	●	●	●	●	●
Improvement in adherence to antibiotic duration of therapy recommendations for uncomplicated cystitis: a quasi-experimental study. Giancola SE, et al. (2019)	●	●	●	●	●	●
Systematic Review and Meta-analysis to Estimate the Antibacterial Treatment Effect of Nitrofurantoin for a Non-Inferiority Trial in Uncomplicated Urinary Tract Infection. Mitrani-Gold FS, et al.	●	●	●	●	●	●

Domains:

- D1: Bias due to randomization
- D2: Bias due to deviation from intended intervention
- D3: Bias due to missing data
- D4: Bias due to outcome measurement
- D5: Bias due to selection of reported result

Judgement:

● High

● Some concerns

● Low

Abbreviations

AUC: acute uncomplicated cystitis

DOT: duration of treatment

EHR: electronic health records

FDA: Food and drug administration

FM: Fosfomycin

FQ: Fluoroquinolones

IDSA: Infectious Disease Society of America

NTF: Nitrofurantoin

NYS: New York State

PCP: Primary care provider

QALM: quality-adjusted-life-months

RCT: Randomized Control Trial

SMX-TMP: sulfamethoxazole-trimethoprim

UTI: urinary tract infection

uUTI: uncomplicated urinary tract infection