Appendix

Table 2

*Evaluation Table for Critical Appraisal*

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| **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 Findings** |
| 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 costProbabilities- 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-analysisResistance rates for FM were obtained from Antimicrobial Resistance Epidemiological Survey on cystitis. | The analysis revealed that the cost per patient for uUTI treatment is similar for all 4 antibiotics, from $96.19 for sulfonamides to $105.12 for FM. FM 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 levelThe 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%, FM 3g once and NTF 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 FM 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 community pharmacists.Sanyal et al. (2019) | A decision analytic model was used to compare costs and outcome of community pharmacist-initiated management of uUTI to family or emergency physician-initiated management. | Prospective Study of community pharmacists in New Brunswick, Canada 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 | Cure rates and utilities were derived from published studies. Cost of antibiotic treatment and health services use were 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 uUTI.Physician initiated- physician prescribed antibiotics to women presenting with uUTI. | Cost-effectivenessSensitivity to cure ratesSocietal perspective | Using prescribing guidelines, community pharmacist in New Brunswick, Canada prescribed 88%, 8% and 2% of NTF, TMP-SMX, and FM respectively, while physicians prescribed 55%, 26%, and 2% of NTF, TMP-SMX, and FM respectively. All patients were assumed to achieve resolution of symptoms in one month including those who received second round of treatment. | The community pharmacist-initiated and guided management was less costly and gave comparable QALMs compared to family and emergency physicians in prescribing NTF, TMP-SMX, or Fosfomycin for the treatment of uncomplicated UTIs. | High |
| Qualitative Analysis of Primary Care Provider Prescribing Decisions for Urinary Tract Infections[Grigoryan](https://pubmed.ncbi.nlm.nih.gov/?term=Grigoryan+L&cauthor_id=31248119) 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 prescribed TMP-SMX or NTF but sometimes longer duration than recommended by the 2010 IDSA; providers described multiple consideration when prescribing antibiotics; many providers mentioned that NTF is not as “strong” and not as “quick”; most providers were unfamiliar with FM; few providers directly relied on guidelines; only two providers recalled and mentioned the IDSA guidelines; providers had widely differing opinions on the extent to which antibiotic resistance is a problem in their own practices. | Few providers relied on IDSA guideline in the treatment of uncomplicated UTIs. | Good |
| 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 $x^{2} $test or Fisher’s exact test. | IDSA guidelines:NTF, SMX-TMPT, and FM were categorized as first-line agents.B-lactams and FQ are categorized as others. | Counts and proportion were used to describe the year-specific overall prescribing rate for each antibiotic category. | The $x^{2}$ 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 NTF, TMP-SMX, and FM prescription and B lactamase prescriptions increased, and FQ 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 NTF and FM. | Multinational, open-label, analyst-blinded, randomized clinical trial. | 513 non-pregnant women aged 18 years and older with symptoms of AUC 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 therapyFailure- need for additional of change in antibiotic treatment due to UTI or lack of efficacySecondary outcomes- bacteriostatic response and incidence of adverse events. | Statistical analysis with 95% confidence interval.Primary and secondary outcomes were calculated using$x^{2} $tests. | At 28 days, 171 of 244 (70%) of the NTF group and 139 of 241 (58%) achieved clinical resolution. Microbiologic resolution occurred in 129 of 175 (74%) and 103 of 163 (63%) in the NTF and FM groups, respectively. | 5-day NTF significantly has higher clinical and microbiological resolution than single-dose FM, 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, 367 outpatient E. coli isolates. | Main outcomes- changes in FQ and NTF use and resistance among E. coli isolates.Secondary outcome-change in total outpatient use, appropriateness of FQ prescription, and occurrence of UTI-related clinical events in the 28 days after the index visit. | Manual review of medical records of 100 randomly selected patients prescribed FQs. Electronic laboratory data were expressed for E. coli isolates resistant to FQs or NTF overtime. | Time series analysis. Jan 2003-Jan 2007 when FQ were recommended as first-line therapy for acute uUTI andJul 2007- Dec 2012 when NTF was recommended.Autoregressive integrated moving average, correlation, and Chi-square test were for analyses. | After a change in the institutional guidelines, there was an immediate 26% reduction in FQ use and stabilization in FQ resistant E. coli. There was an increased use of NTF use without a change in NTF resistance.  | High |
| 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 NTF, ciprofloxacin, or levofloxacin for uncomplicated cystitis | Appropriateness of NTF or FQ 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 NTF and 172 were given FQ. 343 or 86.8% and 18 or 10.5% were appropriately prescribed NTF and FQ, respectively. For women inappropriately FQ, 15 or 87.8% lack contraindication to NTF. | The study suggests the need for additional intervention and education to improve and decrease use of FQ. | 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 treatmentSafety 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). | FM trometamol is associated with high patient compliance and is as effective and safe in comparison to comparator antibiotic in the treatment of AUC  | High |
| 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 NTF, 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 EHR. One day in-service/ education was part of the interventions.Duration of treatment (DOT)- 5 days for NTF, 3 days for TMX-SMT, FM 1 dose, and 3 days for Ciprofloxacin. | Pre and post intervention periods were assessed. Chi-square or Fisher’s exact test, and Cochran Armitage Trend test were used to analyze nominal data. Student’s t-test was used to analyzed continuous data. Two tailed P-values ≤0.05 were considered significant. | A total of 787 patients in the pre-intervention and 862 patients in post intervention were compared. After intervention, the adherence rate to the recommended DOT for NTF 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. | Clinics which received education 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. | High |
| 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) |  | Systemic literature review and meta-analysis. | Search resulted in a total of 2048 publications. Of these 76 met eligibility criteria. After inclusion and exclusion, 12 studies, including 11 trials were included in meta-analysis. | Microbiological response- As per FDA guidance, defined as reduction of bacterial uropathogen recovered at study entry to <10³ or at by at least 1-log decrease (CFU/ml) on quantitative urine culture at the test-of-cure-visit. | The study estimated the microbiological response rate for NTF 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% CI were presented in forest plots. | The overall microbiological response (95% confidence interval) was 0.766 (0.665, 0.867) for NTF and 0.342 (0.288, 0.397) for placebo. | The corresponding treatment effect estimate for NTF supports the conservative non-inferiority margin of 12.5% and is consistent with the recently published FDA guidance. | High |