Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infection Among Filipino Children and Adults

Update of the 2013 Philippine CPG on the Diagnosis and Management of UTI in Adults by the Philippine Society for Microbiology and Infectious Diseases

September 2023

Disclaimer and Contact Information

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of urinary tract infection. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

Contact Us

Send us an email at **esel_pile@yahoo.com** for any questions or clarifications on the outputs and process of this Philippine UTI CPG.

Acknowledgements

The Philippine CPG on the Diagnosis and Management of UTI in Children and Adults funded by the Department of Health's (DOH) – National Practice Guidelines Program through Disease Prevention and Control Bureau – Evidence Generation and Management Division.

This project was implemented under the National Kidney and Transplant Institute. It was completed with the esteemed contribution of people representing the different stakeholders.

Participating Societies, Organizations, Agencies and/or Institutions

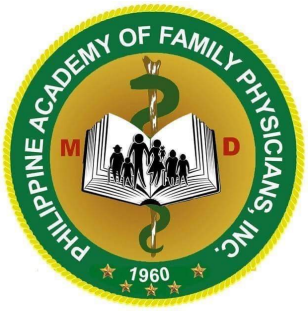

Table of Contents

List of Abbreviations

ADE	Adverse Drug Event
AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AUC	Acute Uncomplicated Cystitis
AUP	Acute Uncomplicated Pyelonephritis
AUROC	Area Under the Receiver Operating Characteristic
BID	Bis in die (Two times a day)
CFU	Colony Forming Units
CI	Confidence Interval
COE	Certainty of Evidence
COI	Conflict of Interest
CP	Consensus Panel
CPG	Clinical Practice Guideline
cUTI	Complicated UTI
CV	Curriculum Vitae
DCOI	Declaration of Conflict of Interest
DOH	Department of Health
ERE	Evidence Review Experts
GRADE	Grading Recommendations, Assessment, Development and Evaluation
HPF	High Power Field
IV	Intravenous
NOS	Newcastle-Ottawa Scale
NPG	National Practice Guidelines
OR	Odds Ratio
PAC	Proanthocyanidin
PICO	Population, Intervention, Comparator, Outcome
PO	Per Orem
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QID	Quarter in die (Four times a day)
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
ROB 1	Risk of Bias Assessment Tool Version 1
rUTI	Recurrent UTI
SC	Steering Committee
SD	Standard Deviation
SR	Systematic Review
TC	Technical Coordinators
TFCOIRC	Task Force COI Review Committee
TID	Ter in die (Three times a day)
TMP-SMX	Trimethoprim-Sulfamethoxazole
UTI	Urinary Tract Infection
WBC	White Blood Cell

List of Tables

List of Figures

Executive Summary

Urinary Tract Infections (UTI) is one of the top three leading causes of morbidity among Filipinos, according to data from the 2019 Philippine Health Statistics. It poses as a health burden, as it affects both the adult and pediatric populations across all regions of the country. In terms of mortality, diseases of the genitourinary tract are among the top ten in the list of causes. In this regard, the output of this CPG was to address the need for evidence-based management of urinary tract infection therefore leading to outcomes that would reduce its impact on the morbidity and mortality in the country.

This guideline was based on the current best available evidence, local resources, infrastructure, and practice context in the country. Guideline recommendations were developed following a standard guideline development methodology outlined in the DOH CPG Manual 2018. Separate working groups were formed. Existing evidence were comprehensively searched and reviewed to address ten key questions. A multisectoral panel of representatives and experts crafted consensus recommendations. The GRADE method was used to determine the direction and strength of each recommendation.

A total of 14 recommendations were developed out of 10 clinical questions and their corresponding evidence summaries. Of these, majority were weak recommendations with one strong recommendation. These recommendations were based on very low to low certainty of evidence. Further research will very likely have a significant impact in our confidence regarding the estimates of the effect of each intervention, or accuracy and precision of the diagnostic tests mentioned in this CPG.

Summary of Recommendations

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
1	Among symptomatic adult (d*ysuria, frequency, urgency, gross hematuria, nocturia, and without vaginal discharge and/or vaginal irritation*), non-pregnant, women, we recommend against the use of urine dipstick or urinalysis in diagnosing acute uncomplicated cystitis.	Low ⊕⊕◯◯	Strong
2	Among symptomatic adult (*fever, flank pain, chills, dysuria, or combination of fever and flank pain, chills, or dysuria*), we suggest the use of urinalysis, with or without nitrite and leukocyte esterase, to diagnose uncomplicated pyelonephritis.	Low ⊕⊕◯◯	Weak
3A	Among symptomatic children 5 years old and younger, we suggest the use of urinalysis, with or without leukocyte esterase and nitrites, in the diagnosis of urinary tract infection prior to initiation of treatment.	Low ⊕⊕◯◯	Weak
3B	Among symptomatic children above 5 years old, we suggest the use of urinalysis, with or without leukocyte esterase and nitrites, in the diagnosis of urinary tract infection prior to initiation of treatment.	Very Low ⊕◯◯◯	Weak
4	Among adult patients diagnosed with acute uncomplicated cystitis, we suggest the use of the following oral antibiotics: • Fosfomycin • Nitrofurantoin • Alternative – Cephalosporin (2nd and 3rd generation), Co-Amoxiclav, Cotrimoxazole* (if culture shows susceptibility)	Low ⊕⊕◯◯	Weak
	Foot note: *Some suggested dose and duration of antibiotics for treatment of adult AUC are as follows:* ○ *Fosfomycin trometamol 3g single dose per orem (PO).* ○ *Nitrofurantoin macrocrystals 100mg QID for 5 days PO.* ○ *Cefuroxime 250mg to 500mg BID for 7 days PO.* ○ *Cefaclor 500mg TID for 7 days PO.* ○ *Cefixime 200mg BID for 7 days PO.* ○ *Cefpodoxime proxetil 100 mg BID for 7 days PO.* ○ *Ceftibuten 200mg BID for 7 days PO.* ○ *Co-amoxiclav 625mg BID to TID for 7 days PO.* ○ *TMP-SMX 160/800 ng BID for 3 days PO.* *Review local and institutional antibiograms, if available.* *Adjust dose depending on GFR.*		
5	We suggest starting with a course of oral fluoroquinolones among adult patients with acute uncomplicated pyelonephritis.	Low ⊕⊕◯◯	Weak
	Footnote: *Some suggested dose and duration of antibiotics for treatment of adult AUP are as follows:* ○ *Ciprofloxacin 500mg BID for 7-10 days PO.* ○ *Ciprofloxacin extended release 1000mg OD for 7 days PO.* ○ *Levofloxacin 250mg OD for 7-10 days PO.* ○ *Levofloxacin 750mg OD for 5 days PO.* ○ *Ofloxacin 400mg BID for 14 days PO.* *Use of fluoroquinolones should be evaluated for clinical response (i.e., afebrile, symptom improvement) after 48 hours of therapy. Patient should be admitted if with no improvement as to avoid delay of management.* *Urine culture and sensitivity study should be performed prior to antibiotics so that the healthcare provider can shift treatments if needed.* *Moxifloxacin is not recommended due to low antibiotic concentration in the urine.* *Review local and institutional antibiogram, if available.*		
6A	We recommend the use of oral antibiotics for the treatment of acute urinary cystitis in children.	Best Practice Statement	
6B	We suggest either short course (3-7 days) or conventional 10-day course of oral antibiotics for the treatment of acute uncomplicated cystitis in children.	Very Low ⊕◯◯◯	Weak
6C	We suggest the following antibiotics in the management of acute uncomplicated cystitis in children:	Very Low ⊕◯◯◯	Weak

	• Nitrofurantoin • Ampicillin-Sulbactam • Amoxicillin-Clavulanic acid • Cefuroxime		
	Footnote: *Some suggested dose and duration of antibiotics for treatment of pediatric AUC are as follows:* o *Nitrofurantoin 5-7 mg/kg/day divided into 3 to 4 divided doses PO.* o *Co-amoxiclav 30-50 mg/kg/day in 2 divided doses PO.* o *Cefuroxime 20-30mg/kg/day in 2 divided doses PO; same with adult dosing if ≥40kg.* o *Ampicillin-sulbactam: Ampicillin 100mg/kg/day divided in 4 doses IV if oral medications are not tolerated.* *Review local and institutional antibiograms, if available.* *Antibiotic treatment should be switched appropriately as soon as culture study results are available.*		
7A	We suggest the use of either short course (3-4 days) intravenous antibiotics followed by oral antibiotics or oral antibiotics to complete 7-10 days treatment duration for children with acute pyelonephritis.	Low ⊕⊕◯◯	Weak
7B	We suggest the use of the following antibiotics as empiric treatment regimen for children with acute pyelonephritis: • Ampicillin-Sulbactam • Cefuroxime • Ceftriaxone • Cefixime • Co-amoxiclav • Amikacin (for those with beta-lactam allergies)	Low ⊕⊕◯◯	Weak
	Footnote: *Some dosage and duration of antibiotic treatment for pediatric AUP are as follows:* o *Nitrofurantoin 5-7 mg/kg/day divided into 3 to 4 divided doses PO.* o *Ampicillin-sulbactam: Ampicillin 100mg/kg/dose in 4 divided doses IV.* o *Co-amoxiclav 30-50 mg/kg/day in 2 divided doses PO.* o *Cefuroxime 20-30 mg/kg/day in 2 divided doses PO; same with adult dosing if ≥40kg.* o *Ceftriaxone 50-75 mg/kg/day in 2 divided doses IV.* o *Cefixime suspension 8 mg/kg/day in 2 divided doses PO.* o *Amikacin 15-22.5 mg/kg/day divided in 2 to 3 doses IV.* *Review local and institutional antibiograms, if available.* *Antibiotic treatment should be switched appropriately as soon as culture study results are available.*		
8	Among adult women with recurrent UTI, we suggest the use of antibiotic prophylaxis after maximizing all other preventive measures.	Low ⊕⊕◯◯	Weak
	Footnote: *Review local and institutional antibiograms, if available.* *Some antibiotics that have been used for prophylaxis are as follows:* o *Fosfomycin 3g sachet, 1 sachet every 10 days* o *Nitrofurantoin 100 mg tab, 1 tab ODHS* o *Cefalexin 250 mg cap, 1 cap OD* o *Norfloxacin 200 mg tab OD* o *Trimethoprim-sulfamethoxazole 40mg/200mg cap, 1 cap ODHS*		
9	Among women with recurrent UTI, we suggest cranberry products.	Low ⊕⊕◯◯	Weak
10	Among children and adults with recurrent UTI, we recommend referral to a higher level of care.	Best Practice Statement	

Introduction

Background

Urinary tract infections (UTI) are among the leading indications for seeking healthcare in the community. It affects both the pediatric and adult populations. The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults was first published in 1998 and revised in 2004 to provide primary care physicians and specialists with evidence-based recommendations on the care of patients with UTI. In 2014, an updated version of the guideline included topics on Asymptomatic Bacteriuria, Recurrent UTI, and Complicated UTI. This current CPG incorporates evidence from the available medical and scientific literature since that time.

The Universal Healthcare Law of the country aims to provide the healthcare needs of everyone. As we transition towards its full implementation in primary care settings, health care professionals could benefit from the guidance of this document in the management of UTI in pediatric and adult populations.

Objectives

The objective of this project is to create clinical practice guidelines for the management of adult and pediatric Filipino patients with urinary tract infection in the outpatient setting, using appropriate scientific information and economic implications of diagnostic tests and pharmacologic treatment.

General Objectives:

1. To determine the tests needed in the diagnosis of urinary tract infection among Filipino adults and children.
2. To determine the pharmacologic management of urinary tract infection among Filipino adults and children
3. To determine the pharmacologic and non-pharmacologic strategies in the prevention of recurrent urinary tract infection among Filipino adults and children

Scope and Purpose

The focus of the guideline is on the diagnosis, treatment, and prevention of UTI in adults and children in the outpatient setting. The guideline does not cover diagnosis and management of complicated UTI or UTI requiring specialized diagnosis and treatment. The guidelines are not intended to replace a healthcare professional's conscious clinical judgement. Possible variations in clinical presentation, presence or absence of comorbidities, or availability of resources may require adjustments of the recommendations.

Target Population

This CPG is intended to be applied to primarily adult and pediatric Filipinos diagnosed with or at risk of UTI in the outpatient setting. The severity was indicated in recommendations with severity-specific questions. Other clinical characteristics, such as comorbidities, that would affect the recommendations are appropriately and clearly indicated.

Intended Users

This CPG aims to guide General Practitioners, Family Medicine Physicians, General Internists (Internal Medicine), General Pediatricians, Doctors to the Barrios (DTTB), Fellows and Residents in training, and Medical Students in the diagnosis and treatment of Urinary Tract Infection in the outpatient setting. Barangay health workers and nurses in local rural health units or barangay centers may benefit from the guidance regarding non-pharmacologic preventive measures.

Key Clinical Issues and Questions

The following clinical issues were addressed by this CPG:

Question 1. Among symptomatic adults (dysuria, frequency, urgency, gross hematuria, nocturia, and without vaginal discharge and/or vaginal irritation), should we use urinalysis to confirm diagnosis of Acute Uncomplicated Cystitis (AUC) prior to initiation of treatment?

Population	Non-pregnant, immunocompetent, premenopausal adult women
Intervention / Exposure	Urinalysis
Comparison	Symptoms
Outcome(s)	Presence of UTI (culture), clinical outcomes
Brief Rationale / Context	To evaluate the need of using urinalysis when diagnosing AUC among adult patients to prevent the irrational use of antibiotics in the advent of antimicrobial resistance and antibiotic stewardship.

Question 2. Among symptomatic adults (presenting with fever, flank pain, chills, dysuria, or combination of fever and flank pain, chills, or dysuria), should we recommend urinalysis to confirm the diagnosis of Acute Uncomplicated Pyelonephritis (AUP) prior to initiation of treatment?

Population	Adults presenting with symptoms of fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness, with or without symptoms of lower urinary tract infection
Intervention / Treatment	Urinalysis
Comparison	Clinical presentation only
Outcome(s)	Diagnosis of AUP, resolution of symptoms, improvement of symptoms, progression of symptoms, complication, sepsis, morbidity, adverse events, antibiotic change, and cost
Brief Rationale / Context	To evaluate the need of using urinalysis when diagnosing AUP among adult patients to prevent the irrational use of antibiotics in the advent of antimicrobial resistance and antibiotic stewardship.

Question 3. Among symptomatic children (presenting with fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness with or without symptoms of lower urinary tract infection), should we recommend urinalysis to confirm the diagnosis of Urinary Tract Infection prior to initiation of treatment?

Population	Symptomatic children presenting with fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness with or without symptoms of lower urinary tract infection
Intervention / Treatment	Clinical judgment and urine examination (urine dipstick)
Comparison	Clinical judgment alone
Outcome(s)	Diagnosis of UTI, cost, incidence of recurrent UTI, end stage renal disease
Brief Rationale / Context	To evaluate the need of using urinalysis when diagnosing UTI among pediatric patients to prevent the irrational use of antibiotics in the advent of antimicrobial resistance and antibiotic stewardship.

Question 4. Among adult patients diagnosed with Acute Uncomplicated Cystitis (AUC), should we recommend antibiotics for treatment?

Population	Adult patients diagnosed with AUC
Intervention / Treatment	Oral antibiotics (nitrofurantoin, fosfomycin, quinolones, amoxicillin, ampicillin, trimethoprim-sulfamethoxazole, beta lactams)
Comparison	No antibiotics / placebo
Outcome(s)	Clinical improvement, microbiological success, recurrence of UTI, worsening of events and adverse events
Brief Rationale / Context	This is to help address if antibiotic treatment should be given in adult patients with AUC in the advent of antibiotic resistant pathogens.

Question 5. Among adult patients diagnosed with Acute Uncomplicated Pyelonephritis (AUP), should we recommend antibiotics for treatment?

Population	Adult patients diagnosed with AUP
Intervention / Treatment	Oral antibiotics (fluoroquinolones, cephalosporin, beta lactams trimethoprim-sulfamethoxazole)
Comparison	No antibiotics / placebo
Outcome(s)	Resolution of AUP, improvement of symptoms, progression of symptoms, morbidity, adverse drug reactions, costs, antibiotic resistance
Brief Rationale / Context	This is to help address if antibiotic treatment should be given in adult patient with AUP since there are significant complications that may lead to renal scarring and renal insufficiency if AUP is not treated adequately.

Question 6. Among pediatric patients diagnosed with Acute Uncomplicated Cystitis (AUC), should we recommend antibiotics for treatment?

Population	Pediatric patients diagnosed with AUC
Intervention / Treatment	Antibiotics
Comparison	No antibiotic, placebo, antibiotic other than intervention
Outcome(s)	Resolution of AUC, improvement of symptoms, progression of symptoms, complications, morbidity, adverse events, costs, antibiotic resistance, drug-drug interactions, adherences
Brief Rationale / Context	This is to help address if antibiotic treatment should be given in pediatric patients with AUC in the advent of antibiotic resistant pathogens.

Question 7. Among pediatric patients diagnosed with Acute Uncomplicated Pyelonephritis (AUP), should we recommend oral antibiotics for treatment?

Population	Pediatric patients diagnosed with AUP
Intervention / Treatment	Antibiotics
Comparison	No antibiotic, placebo, antibiotic other than intervention
Outcome(s)	Resolution of AUP, improvement of symptoms, progression of symptoms, complications, morbidity, adverse events, cost, antibiotic resistance, drug-drug interactions, adherence
Brief Rationale / Context	This is to help address if antibiotic treatment should be given in pediatric patients with AUP, as inadequate treatment may lead to further complications such as renal scarring and end-stage renal disease.

Question 8. Among adult patients with recurrent UTI, should we recommend giving antibiotics as prophylaxis?

Population	Adult patients with recurrent UTI
Intervention / Treatment	Antibiotic prophylaxis
Comparison	Placebo or no antibiotic prophylaxis
Outcome(s)	Prevention of recurrent UTI, resolution of recurrent UTI, improvement of symptoms, progression of symptoms, complications, morbidity, adverse events, drug-drug interactions, and cost
Brief Rationale / Context	This is to help address if antibiotic treatment should be given in patients with recurrent UTI, knowing the growing concern about antibiotic resistance.

Question 9. Among patients with recurrent UTI, should we recommend cranberry as a preventive measure?

Population	Patients with recurrent UTI
Intervention / Treatment	Cranberry
Comparison	None / Placebo
Outcome(s)	Worsening if symptoms, complications, mortality, antibiotic resistance, improvement of symptoms, adherence, adverse events, drug-drug interactions, and cost
Brief Rationale / Context	While antibiotic prophylaxis has been proven to be beneficial in some patients, there is an advantage in exploring other treatment option such as using cranberry to decrease the frequency of recurrent UTI to address the burden of antimicrobial resistance.

Question 10. Among patients with recurrent UTI, what are the indications (i.e., predisposing conditions, risk factors) for referral to a higher level of care?

Population	Patients with recurrent UTI
Intervention / Treatment	Indication for referral: recurrent UTI, complicated UTI, no response to initial treatment, with findings on imaging procedure
Comparison	None / Placebo
Outcome(s)	Improvement of symptoms, antibiotic resistance, cure rate / resolution, progression of UTI, mortality, complications / morbidity, adverse events, adherence to medications, cost
Brief Rationale / Context	A certain proportion of patients may present with recurrent urinary tract infections and may pose a dilemma to the general physician. In most cases, there is a secondary cause such as an anatomic abnormality or established systemic illness or secondary immune defects due to other medical disorders. Delay in diagnosis may complicate initial simple problems and may entail a corresponding increase in morbidity, and costs of work-ups and treatment.

CPG Development Methodology

Guideline Preparation

COMPOSITION OF CPG TASK FORCE

The Steering Committee (SC) was composed of members representing one or more of the following expertise: CPG methodology, adult nephrology, pediatric nephrology, infectious diseases, and urology. Aside from clinicians, there were also representatives from the DOH. All members have technical knowledge and expertise on clinical management and policy related to UTI. The Steering Committee invited relevant professional organizations to nominate individuals who can become part of the consensus panel. Selected experts, by virtue of their training background and experience in critical appraisal and guideline development, were also invited by the SC to serve as Evidence Review Experts.

The Evidence Review Experts (ERE) were composed with one or more of the following expertise: methodologists, clinical epidemiologists, evidence-based medical practitioner. They had previous training and expertise and experience in CPG development and evidence synthesis. Evidence Review Experts reviewed and appraised existing CPGs, systematic reviews, preprints, and published literature recommendations. One Technical Coordinator with expertise in CPG development and evidence-based medicine oversaw the retrieval and appraisal of evidence and the creation of the draft recommendations. One Technical Writer ensured that the evidence summaries are uniform, clear, and concise. The Steering Committee organized several practice sessions for the ERE to finalize their presentations, and discuss them with other EREs, the Steering Committee, and the technical experts. Evidence summaries were collated, formatted, and prepared for presentation to the consensus panel.

The Consensus Panel (CP) was composed of multi-sectoral representatives such as health practitioners, both specialists and non-specialists, and patient advocates. All panel members represented different institutions including: The National Kidney and Transplant Institute, Philippine College of Physicians (PCP), Philippine Society of Nephrology Inc. (PSN), Pediatric Nephrology Society of the Philippines (PNSP), Philippine Society for Microbiology and Infectious Diseases (PSMID), Philippine Academy of Family Physicians (PAFP), Philippine Pediatric Society (PPS), and Philippine Alliance of Patient Organizations (PAPO). There were also representatives from the Department of Health. They were designated as representatives of the relevant professional groups and stakeholder organizations and were selected based on their content expertise and experience, as well as their conflict of interest. The panelists, being involved directly in UTI patient care, and may have direct experienced of the disease itself, acted also on behalf as patient advocates to help reflect public's views and preferences.

Refer to Appendix 1 for the full composition of CPG task force of the Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Children and Adults. Their declarations of conflicts of interest are presented in Appendix 2.

Evidence Synthesis

SEARCH METHODS AND STRATEGIES

A systematic search of electronic databases, including but not limited to, MEDLINE via PubMed, CENTRAL, and Google Scholar was performed; free search via Google search was done. Other accessible bibliographic databases, trial registers, preprint servers were searched. Existing systematic reviews and meta-analyses were examined to extract the primary studies. Local authors and experts were contacted for research outputs being done in the country.

No time limit was imposed on the search in general. Only English language or English-translated studies were included.

INCLUSION AND EXCLUSION CRITERIA

In general, the following evidence were included:

- Primary research that enrolled adults and/or children with UTI, Acute Uncomplicated Cystitis, Acute Uncomplicated Pyelonephritis, or Recurrent UTI
- Primary research on the diagnostic accuracy of urinalysis for UTI
- Primary research on the efficacy and safety of antibiotics for the treatment of UTI, Acute Uncomplicated Cystitis, or Acute Uncomplicated Pyelonephritis, or for the prevention of Recurrent UTI
- Primary research on the efficacy and safety of cranberry as non-pharmacologic preventive measure for Recurrent UTI
- Primary research that investigated as outcomes resolution of the problem, improvement of symptoms, progression of symptoms or condition, recurrence of problems, need for admission, complications, adverse events, cost-effectiveness, etc.
- Systematic reviews and meta-analysis, or clinical practice guidelines, that included any of the above
- Local antibiograms in the Philippines (national, regional, or institutional level)
- For efficacy and safety questions, randomized controlled trials were given preference; for other questions, non-RCT were included.

STUDY QUALITY ASSESSMENT

Assessment of quality and risk of bias of all studies eligible for inclusion were performed by the two EREs assigned to each question. In the case of non-concurrence, the technical coordinator resolved the disagreement.

Appraisal tools, as appropriate for the study design, were used: Risk of Bias Assessment Tool Version 1 (ROB 1) for randomized controlled trials. Newcastle-Ottawa Scale (NOS) for cohort studies, Quality Assessment of Diagnostic Accuracy Studies (QUADAS) for studies investigating diagnostic accuracy, A Measurement Tool to Assess Systematic Reviews (AMSTAR) for systematic reviews and meta-analysis, and Appraisal of Guidelines for Research and Evaluation II (AGREE-II) tool for clinical practice guidelines.

The overall certainty of evidence for outcomes deemed critical for decision-making were assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). (See Table A)

Recommendations for each question were based on the burden of the condition, balance between benefits and harms of intervention, certainty of evidence, values and preferences, resource requirements, cost-effectiveness, and impact on health equity.

Table A. Factors influencing certainty of evidence (COE).

Certainty of Evidence	Study Design – Intervention Questions	Study Design – Diagnosis Questions	Factors that Decrease COE (by 1 to 2 levels)	Factors that Increase COE (by 1 to 2 levels)
High	Randomized controlled trial	Systematic Reviews and Meta-analysis Appropriate cross-sectional or cohort studies in patients with diagnostic uncertainty	• Risk of Bias • Inconsistency • Indirectness • Imprecision • Publication Bias	• Large magnitude effect • Plausible confounding • Dose-response gradient
Moderate	-	-		
Low	Observational study	-		
Very Low	-	-		

DATA SYNTHESIS

All evidence were synthesized qualitatively by a narrative description and a tabulation of pertinent details of included studies. When proper and applicable, quantitative synthesis was performed using RevMan 5.4.3, STATA, or MetaDTA.

Formulating Recommendations

Recommendations were formulated using the Evidence to Decision framework of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

The multi-sectoral consensus panel (CP) was responsible in formulating the recommendations through consensus on the wording, direction an strength of the guidance. The recommendations were based on the following primary considerations: quality of the evidence, balance between benefits and harms, test accuracy, values, preferences, and burden on patients, cost and resource use, equity, feasibility, and acceptability.

CERTAINTY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

The certainty of evidence was one of the bases of the consensus panel in making the final recommendation. The strength of each recommendation (i.e., strong, or weak) was determined by the panel considering all the factors mentioned above. *Strong*

recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects”, while *Weak recommendation* means that the “desirable effects of adherence to a recommendation probably outweigh the undesirable effects but is not confident”.

Table B and C show the definition and implication of each:

Table B. GRADE certainty of evidence definition and implication.

GRADE Certainty of Evidence	Definition	Implication
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change confidence in the estimate of effect
Moderate ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low ⊕⊕◯◯	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very Low ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	Any estimate of effect is very uncertain

Table C. Implications of the Strength of Recommendation to Patients, Clinicians, and Policymakers.

	Strong Recommendation	Weak Recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for different patients. Clinicians must help each patient arrive at a management decision consistent with her or his values and preferences.
Policy Makers	The recommendation can be adopted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and the involvement of many stakeholders. Policies are also more likely to vary between regions.

PATIENT'S VIEWS AND PREFERENCES

Patient views and preferences were presented by the patient representative / nurse who had direct patient care. Additionally, the consensus panel members who were directly involved in various aspects of UTI care such as: clinicians, administrators, and researchers, were also accounted. This strategy guaranteed that patient views and

preferences were still considered in formulating the recommendations. Relevant literature was also searched and discussed, when available.

RESOURCE IMPLICATIONS

The consensus panelists took into consideration the local cost of the different interventions of interest in the different practice contexts, and the resources required for the proper implementation of the recommendations.

CONSENSUS PROCESS

The recommendation for each question and its strength was finalized through voting. A consensus decision was reached when 75% of voting CP members had agreed. Thus, a consensus threshold was set at 7 or 8 out of the 9 or 10 present voting members, respectively. Discussions and questions were encouraged when a consensus was not reached after the first round of voting. Two more rounds of voting were conducted if an issue regarding the recommendation was not resolved. A modified Delphi panel method was used when there was failure to reach consensus after three rounds of nominal voting.

Guideline Dissemination

The final CPG manuscript on UTI will be submitted to the National Practice Guidelines Clearinghouse of the DOH for quality appraisal. Once reviewed and approved, the manuscript will then be adopted as a national practice guideline.

The dissemination of the CPG will be done through a launching activity through a national and official DOH initiated event or forum. Subsequently, dissemination of the CPG will be done in specialty societies-initiated forums or conferences.

DOH shall be responsible in generating the official online copy as well as the printing of the manuscript for dissemination to the stakeholders. The UTI CPG Task Force Steering Committee will oversee setting the specific set of quality indicators to guide the DOH in monitoring and evaluation.

Guideline Monitoring and Evaluation

The guideline implementation will be assessed by measuring adherence of healthcare providers and institutions to the recommendations of the Philippine CPG on the Diagnosis and Management of UTI in Children and Adults. The impact on clinical outcomes such as reduction in morbidity and mortality in quality assurance studies, clinical pathway compliance reviews, and operational research will be used for evaluation. This will be done in collaboration with different professional societies and healthcare institutions.

External Review

The completed manuscript was subjected to an external review which was facilitated by two external reviewers specifically a methodologist (1) and a content expert (1). The methodologist ensured that the methodological aspects of the CPG development was followed according to quality standards in research, including its reporting using the AGREE-II checklist. The content expert oversaw the technical aspects of the CPG

recommendations using the AGREE-REX checklist. Comments sought from the external review were discussed among the steering committee members, technical coordinators, and technical adviser. Corresponding revisions were facilitated.

Guideline Updating

The National Kidney and Transplant Institute, in coordination with the Philippine Society of Nephrology and Philippine Society for Microbiology and Infectious Diseases shall partner with DOH in evaluating the need to update the CPG every 3 years or earlier as deemed necessary.

Editorial Independence

FUNDING SOURCE

This UTI CPG development was funded by the DOH. The UP NIH oversaw the overall management and disbursement of the allocated funds. While the DOH served as a resource for policy in the consensus panel meetings, no representative from the DOH was present as a voting member and thus did not influence in the crafting of the recommendations.

MANAGEMENT OF CONFLICTS OF INTEREST

All members of the CPG Task Force such as the Steering Committee (SC), Evidence Review Experts (ERE), Consensus Panelists (CP), Technical Coordinators, Technical Facilitator, Technical Writer and Administrative Officer underwent screening for conflict of interest by submitting their curriculum vitae (CV) and accomplishing a prescribed Declaration of Conflict-of-Interest (COI) form. A COI Review Committee was created within the UTI CPG Task Force and were composed of two individuals, recommended by the Steering Committee, and approved by the National Practice Guideline (NPG) COI Review Committee (after proper screening of COIs of nominated COI Review Committee members). The Steering Committee and Task Force COI Review Committee (TFCOIRC) underwent training on screening and managing conflicts of interest. The TFCOIRC reviewed the CVs and COI forms of all members of the task force and gave recommendations regarding the extent of participation of the CPG Task Force members. These recommendations were submitted to the Steering Committee who then informed the members of the task force regarding the outcome of the COI assessment and the recommendations for the appropriate management of identified potential conflicts of interest. Certain consensus panelists were prohibited from voting on certain clinical questions if they were deemed to be in a position of significant potential COI in the context of such questions.

REFERENCES

1. Department of Health – Philippines. 2019. The 2019 Philippine Health Statistics. Epidemiology Bureau, Manila. Available from: https://doh.gov.ph/sites/default/files/publications/2019PHS_Final_092121.pdf
2. Task Force on UTI 2013. 2013. Philippine Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013 Update: Part 1. Philippine Practice Guidelines Group in Infectious Diseases Philippine Society for Microbiology and Infectious Diseases. Available from: https://www.psmid.org/wp-content/uploads/2020/03/CPG-UTI-2013-uncomplicated-part1.pdf
3. Task Force on UTI 2015. 2015. Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2015 Update: Part 2. Philippine Practice Guidelines Group in Infectious Diseases Philippine Society for Microbiology and Infectious Diseases. Available from: https://www.psmid.org/diagnosis-and-management-of-urinary-tract-infections-in-adults-2015-update-part-2/
4. Department of Health – Philippines Administrative Order No. 2021-020. 2021. Revised Guidelines on National Practice Guideline Development. Available from: https://law.upd.edu.ph/wp-content/uploads/2021/06/DOH-Administrative-Order-No-2021-0020.pdf
5. Department of Health – Philippines and Philippine Health Insurance Corporation. 2018. Manual for Clinical Practice Guideline Development. Available from: https://www.psmid.org/wp-content/uploads/2021/09/CPG-Manual-First-Edition_2018_27_11.pdf
6. GRADE Handbook. October 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html.

Recommendation and Evidence Summaries

Diagnosis of UTI

Question 1. Among symptomatic adults*, should we use urinalysis to confirm the diagnosis of Acute Uncomplicated Cystitis (AUC) prior to initiation of treatment?

***Dysuria, frequency, urgency, gross hematuria, nocturia, and without vaginal discharge and/or vaginal irritation**

Recommendations

Among symptomatic adult*, non-pregnant, women, we **recommend against** the use of urine dipstick or urinalysis in diagnosing acute uncomplicated cystitis. (***Low certainty of evidence, Strong recommendation***)

**Dysuria, frequency, urgency, gross hematuria, nocturia, and without vaginal discharge and/or vaginal irritation*

Consensus Issues

- The panel noted that the likelihood of AUC is high when multiple symptoms suggestive of UTI (e.g., dysuria, urgency, frequency, hematuria, nocturia) is experienced in the absence of vaginal discharge. Moreover, urinalysis and urine dipstick had very minimal diagnostic utility in such situation.
- The panel gave considerations on significant increase in the likelihood of an accurate diagnosis of AUC with the performance of urinary test in cases where only one symptom is present despite the low quality of evidence. However, the panel decided to give higher value on the harms of potential delay of treatment, cost, and limited accessibility of urine tests. Thus, the panel recommended against it.

KEY FINDINGS

Six observational studies evaluated the diagnostic accuracy of urine tests such as urine dipstick and urine microscopy for urinary tract infection in women with symptoms suggestive of urinary tract infection.

Positive nitrite on urine dipstick or the presence of bacteria on urine microscopy increased the probability of detecting UTI in symptomatic adults. On the other hand, the absence leukocyte esterase on urine dipstick or the absence of WBC on urine microscopy decreased the probability of UTI.

The overall certainty of evidence was low.

INTRODUCTION

Acute uncomplicated cystitis is a lower urinary tract infection in an immunocompetent, pre-menopausal, non-pregnant woman with no urologic abnormalities. The latest Philippine Clinical Practice Guidelines published in 2013 on the diagnosis and management of UTI (by the Task force on UTI 2013, Philippine Practice Guidelines

Group on Infectious Diseases) recommends that urinalysis is not necessary to diagnose acute uncomplicated cystitis. In this era of rising antibiotic resistance, amid efforts to promote antibiotic stewardship among medical practitioners, and at the same time keeping in mind cost and patient convenience, it was deemed necessary to re-evaluate strategies in the diagnosis of acute uncomplicated cystitis.

REVIEW METHODS

A systematic search was done from January 6, 2023, to February 6, 2023, using the following databases: MEDLINE, Cochrane (CENTRAL), Epistemonikos, MedRxiv, BioRxiv, HERDIN, PROSPERO, and Trip Database. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, Chinese Clinical Trial Registry, EU Clinical Trials Register, WHO ITCRP). The following search terms were used: urinary tract infection, cystitis, clinical diagnosis, urinalysis, improvement, outcomes, resolution of symptoms, women. The inclusion criteria for choosing studies were: (1) adult patient with UTI-related symptoms specifically dysuria, frequency, urgency, gross hematuria, malodorous urine with or without vaginal discharge; (2) urinalysis was used to diagnose UTI; (3) comparator was diagnosis of UTI through clinical presentation only without any confirmatory test; (4) outcomes were diagnosis of acute uncomplicated cystitis, resolution of symptoms, improvement of symptoms, progression of symptoms, complications, morbidity, adverse events, and cost. Subgroup analysis was planned, if available, for two groups of patients: (1) normal healthy adults and (2) adults with comorbidities and/or medications. Only studies with free full texts available and in English language were included in this review. Studies which included pediatric patients, pregnant patients, post-operative patients, patients with spinal cord abnormalities and other patients with complicated UTI were excluded.

RESULTS

Diagnostic Accuracy of Urine Test Parameters

Six (6) cross-sectional studies (n= 1340) reported the diagnostic accuracy of urine dipstick using urine culture positivity as the gold standard.[3–7] Five (5) evaluated the presence of nitrites while four (4) studies evaluated the presence of leukocyte esterase through urine dipstick. Three (3) studies also investigated the accuracy of urine microscopy. All the studies included adult patients presenting with symptoms suggestive for UTI such as dysuria, urinary frequency, hematuria, urinary retention, fever and/ or lower abdominal pain. One study also looked at the diagnostic performance of the presence of bacteria. Three (3) studies involve both male and female while the rest were on female.

The diagnostic accuracy of nitrites, leukocyte esterase and pyuria (WBC > 5/hpf) were pooled and presented. The sensitivity and specificity of the presence of nitrites on urine dipstick is 37% (95%CI, 26 to 50) and 94% (95%CI, 0.88 to 0.97), respectively. On the other hand, the sensitivity and specificity of leukocyte esterase is 78% (95% CI, 0.66 to 0.87) and 64% (95% CI, 0.32 to 0.81) respectively. Presence of pyuria defined as WBC of more than 5 per high power field showed a sensitivity of 94% (95% CI, 0.84 to 0.98) and specificity of 46% (95%CI, 0.25 to 0.68). According to the study of Tan[2], bacterial counts of > +1 and +2 had a sensitivity of 0.28 and 0.11 and specificity of 0.95 and 0.99 respectively. (See Table 1.1)

Table 1.1. Diagnostic accuracy of urine test parameters.

URINE TEST	NO. OF STUDIES (N)	SENSITIVITY (95% CI)	CERTAINTY OF EVIDENCE	SPECIFICITY (95% CI)	CERTAINTY OF EVIDENCE
Nitrites	5 (1299)	0.37 (0.26 to 0.50)	Low	0.94 (0.88 to 0.97)	High
Leukocyte Esterase	4 (1103)	0.78 (0.66 to 0.87)	Moderate	0.64 (0.32 to 0.81)	Low
WBC ≥5/hpf	4 (1237)	0.94 (0.84 to 0.98)	High	0.46 (0.25 to 0.68)	Low
Bacterial count ≥+1	1 (564)	0.28 (0.23 tp 0.34)	High	0.95 (0.92 to 0.97)	High

To illustrate the utility of the urine test results, the probabilities after a test based on a single AUC-related symptoms were computed. See Table 2-5. A positive urine dipstick test for nitrite increases the probability of having UTI to at least 90% in patients presenting with a single symptom of dysuria, frequency, urgency, hematuria or nocturia. A negative result on the other hand decreases the probability to around 50% with a single symptom of acute urinary cystitis. (See Table 1.2)

Table 1.2. Pre and post-test probabilities of UTI after testing for urine nitrite.

SIGNS AND SYMPTOMS	PROBABILITY OF HAVING UTI PRIOR TO TESTING (%)	PROBABILITY OF HAVING UTI WHEN URINE NITRITE TEST CAME OUT POSITIVE (%)	PROBABILITY OF HAVING UTI WHEN URINE NITRITE TEST CAME OUT NEGATIVE (%)
Dysuria	62	91	52
Frequency	58	90	48
Urgency	61	91	51
Hematuria	68	93	58
Nocturia	63	91	53
Vaginal Discharge	45	83	35
Dysuria + Absence of Vaginal Discharge	85	96	74
Dysuria + Frequency + Absence of Vaginal Discharge	85	97	79

In patients with any single symptoms of AUC, the presence of leukocyte esterase can increase the probability up above 75%. The absence of leukocyte esterase in patients with a single symptom consistent with UTI can decrease the probability to less than 40%. (See Table 1.3)

Table 1.3. Pre and post-test probabilities of UTI after testing for urine leukocyte esterase.

SIGNS AND SYMPTOMS	PROBABILITY OF HAVING UTI PRIOR TO TESTING (%)[a]	PROBABILITY OF HAVING UTI WHEN URINE LEUKOCYTE ESTERASE TEST CAME OUT POSITIVE (%)	PROBABILITY OF HAVING UTI WHEN URINE LEUKOCYTE ESTERASE TEST CAME OUT NEGATIVE (%)
Dysuria	62	78	36
Frequency	58	75	32
Urgency	61	77	35
Hematuria	68	82	42
Nocturia	63	79	37
Vaginal Discharge	45	64	22
Dysuria + Absence of Vaginal Discharge	83	91	63
Dysuria + Frequency + Absence of Vaginal Discharge	85	92	66

[a] - Pretest probabilities computed from data from the study of Giesen [13]

The absence of WBC decreases the probability to less than 10% while the presence of bacteria in the urine increases the probability to 90%. See tables 1.4 and 1.5.

Table 1.4. Post-test probabilities of UTI after testing for WBC.

SYMPTOM	URINE MICROSCOPY RESULT	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR WBC	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR WBC
Dysuria	WBC ≥ 5/hpf*	62	74	17
	WBC ≥ 10/hpf+		72	15
	WBC ≥ 20/hpf+		75	16
Frequency	WBC ≥ 5/hpf*	58	71	15
	WBC ≥ 10/hpf+		69	7
	WBC ≥ 20/hpf+		72	14
Urgency	WBC ≥ 5/hpf*	61	73	17
	WBC ≥ 10/hpf+		71	8
	WBC ≥ 20/hpf+		74	16
Hematuria	WBC ≥ 5/hpf*	68	79	22
	WBC ≥ 10/hpf+		77	10
	WBC ≥ 20/hpf+		79	20
Nocturia	WBC ≥ 5/hpf*	63	75	18
	WBC ≥ 10/hpf+		73	8
	WBC ≥ 20/hpf+		76	17
Vaginal Discharge	WBC ≥ 5/hpf*	45	59	10
	WBC ≥ 10/hpf+		56	4
	WBC ≥ 20/hpf+		60	9
Dysuria + Absence of	WBC ≥ 5/hpf*	83	89	31

Vaginal Discharge				
Dysuria + Frequency + Absence of Vaginal Discharge	WBC ≥ 5/hpf*	85	91	43

[a]Pre test probabilities computed from data from the study of Giesen [13]

*Based on pooled estimate of 4 studies.

+Based on the study of Tan [2]

Table 1.5. Post-test probabilities of UTI after testing for Bacteria.

SYMPTOM	TEST RESULT*	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR BACTERIA	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR BACTERIA
Dysuria	Bacteria ≥ +1	62	90	55
	Bacteria ≥ +2		95	59
Frequency	Bacteria ≥ +1	58	89	51
	Bacteria ≥ +2		94	55
Urgency	Bacteria ≥ +1	61	90	54
	Bacteria ≥ +2		95	59
Hematuria	Bacteria ≥ +1	68	92	61
	Bacteria ≥ +2		96	65
Nocturia	Bacteria ≥ +1	63	91	56
	Bacteria ≥ +2		95	61
Vaginal Discharge	Bacteria ≥ +1	45	82	38
	Bacteria ≥ +2		90	42
Dysuria + Absence of Vaginal Discharge	Bacteria ≥ +1	83	96	79
Dysuria + Frequency + Absence of Vaginal Discharge	Bacteria ≥ +1	85	97	81

[a]Pre test probabilities computed from data from the study of Giesen [13]

*Based on the study of Tan [2]

CERTAINTY OF EVIDENCE

The studies had an unclear to a high risk of bias, mostly due to lack of clarity whether the reference standard results were interpreted without knowledge of the results of the reference test (Knotterus, Prah, Tan, Tomas, Bellazreg, Charnaya). For the study by

Knotterus, the physician involved in examining the patient was the same person to perform the urine dipstick test. There was high risk of bias for patient selection in the study by Prah.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1.6. Summary of recommendations from other group and agencies.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Scotland NHS Sign 160 Management of Suspected Bacterial Urinary Tract Infection in Adult Women September 2020	Diagnose a UTI in the presence of two or more urinary symptoms (dysuria, frequency, urgency, visible hematuria or nocturia) and a positive dipstick test result for nitrite. Do not diagnose a UTI in the presence of a combination of new onset vaginal discharge or irritation and urinary symptoms (dysuria, frequency, urgency, visible hematuria or nocturia). Do not confirm the diagnosis of a UTI in the presence of a single urinary symptom (dysuria, frequency, urgency, visible hematuria or nocturia).	1+ to 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias and Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
NICE Guidelines for UTI in adults Feb. 15, 2023 [8]	Women aged under 65 years are diagnosed with a urinary tract infection (UTI) if they have 2 or more key urinary symptoms and no other excluding causes or warning signs. Key urinary symptoms: dysuria, new nocturia, cloudy urine *No recommendation about urinalysis	Not applicable
Philippine CPG for UTI in Adults 2013 [9]	Clinically, AUC is suspected in premenopausal non-pregnant women presenting with acute onset of dysuria, frequency, urgency, and gross hematuria, and without vaginal discharge. Urinalysis is not necessary to confirm the diagnosis of AUC in women presenting with one or more of the above symptoms of UTI in the absence of vaginal discharge and complicating conditions	Strong recommendation, high quality of evidence

ONGOING STUDIES AND RESEARCH GAPS

There were no ongoing studies comparing the outcomes of patients who were diagnosed with acute uncomplicated cystitis using urinalysis versus clinical presentation alone. An important research gap identified is the need to investigate clinical patient outcomes in nonpregnant, immunocompetent, and premenopausal women.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

The cost of a routine urinalysis ranges from Php 40 (public hospitals) to Php 350 (private hospital in Metro Manila). A box of 100 urine dipstick strips retails for an average of Php 700.

The cost of the first line antibiotic nitrofurantoin (recommended dose and frequency: 100mg 4x a day for 5 days) is on average Php 1,520.

Patient's values and preference, equity, acceptability, and feasibility

No studies indicating patient values and preferences were found during the literature review.

REFERENCES

1. NHS Scotland. SIGN 160 Management of suspected bacterial lower urinary tract infection in women 2020. Available from https://www.sign.ac.uk/media/1766/sign-160-uti-0-1_web-version.pdf
2. Tan, N., Koonga, A., Nga, L., Hua, P., Koha, E., Tan, K. Moeya, P. Tan, Mei, Wong, C., Tan, T., Hoc, H., Chen, M. Accuracy of urinary symptoms and urine microscopy in diagnosing urinary tract infection in women. Family Practice, 2019, 417–424
3. Knotterus, B., Geerlings, S., Charante, E., Riet, G. Toward A Simple Diagnostic Index for Acute
4. Uncomplicated Urinary Tract Infections. Ann Fam Med 2013;442-451.
5. Bellazreg, F., Abid, M., Lasfar, N, Hattab, Z., Hachfi, W., Letaief, A., Diagnostic value of dipstick test in adult symptomatic urinary tract infections: results of a cross-sectional Tunisian study. The Pan African Medical Journal. 2019;33:131.
6. Chernaya, A., Soborg, C., Midttun, M. Validity of the urinary dipstick test in the diagnosis of urinary tract infections in adults. Dan Med J 2022;69(1):A07210607.
7. Prah, J., Amoah, S., Ocansey, D., Artur, R., Walker, E., Obiri-Yeboah, D. Evaluation of urinalysis parameters and antimicrobial susceptibility of uropathogens among out-patients at University of Cape Coast Hospital. Ghana Med J 2019; 53(1): 44-51
8. Tomas, M., Getman, D., Donskey, C., Heckerd, M. Overdiagnosis of Urinary Tract Infection and Underdiagnosis of Sexually Transmitted Infection in Adult Women Presenting to an Emergency Department. Journal of Clinical Microbiology August 2013 Vol 53 No 8
9. National Institute for Health and Care Excellence. (2023). Urinary Tract Infection in adults [Nice Guideline QS90]. Available from https://www.nice.org.uk/guidance/qs90.
10. Task Force on UTI 2013, Philippine Practice Guidelines Group in Infectious Diseases. (2013). Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013 Update (Part 1). Available from https://www.psmid.org/diagnosis-and-management-of-urinary-tract-infections-in-adults-2013-update-part-1/
11. Medina-Bombardo D, Jover-Palmer A. Does clinical examination aid in the diagnosis of urinary tract infections in women? A systematic review and meta-analysis. BMC Fam Prac 2011;12:111.
12. Meister, L., Morley, E., Scheer, D., Sinert, R. History and Physical Examination Plus Laboratory Testing for the Diagnosis of Adult Female Urinary Tract Infection. Academic Emergency Medicine July 2013, Vol 7 20:632-645

13. Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T.Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Prac 2010;11:

Question 2. Among symptomatic adults*, should we recommend urinalysis to confirm the diagnosis of Acute Uncomplicated Pyelonephritis (AUP) prior initiation of treatment?

***Fever, flank pain, chills, dysuria, or combination of fever and flank pain, chills, or dysuria**

Recommendations

Among symptomatic adult*, we **suggest** the use of urinalysis, with or without nitrite and leukocyte esterase, to diagnose uncomplicated pyelonephritis (***Low certainty of evidence, Weak Recommendation***)

**Fever, flank pain, chills, dysuria, or combination of fever and flank pain, chills, or dysuria*

Consensus Issues

- It was noted by the panel that a WBC ≥5 hpf count on urinalysis has high sensitivity of 99% and is best used to rule out AUP.
- The panel noted that if available and feasible, nitrite and leukocyte esterase determination should be used in the diagnosis of AUP.

KEY FINDINGS

- Seven (7) observational studies evaluated the diagnostic accuracy of a urine dipstick or urine microscopy in the diagnosis of UTI in symptomatic adults.
- Positive nitrite on urine dipstick and the presence of bacteria on urine microscopy increased the probability of detecting UTI in symptomatic adults.
- The overall certainty of evidence of the included studies is low.

INTRODUCTION

Acute uncomplicated pyelonephritis (AUP) is suspected in healthy women with no clinical or historical evidence of anatomic or functional urologic abnormalities. They present with symptoms such as fever (Temp ≥38), chills, flank pain, costovertebral tenderness, nausea and vomiting which may or may not be accompanied by with signs and symptoms of lower tract urinary infection.[1] Other conditions such as sexually transmitted infections, pelvic inflammatory disease, surgical abdomen (i.e., appendicitis), nephrolithiasis or cholecystitis may present with similar symptoms. The determination of the diagnostic utility of a urinalysis in diagnosing AUP can guide clinicians in its management and prevent irrational use of antibiotics. A systematic review of the diagnostic value of individual signs and symptoms has been shown to have a modest ability to rule in or rule out the diagnosis of a urinary tract infection. The use of dipstick tests has been shown to enhance diagnostic utility and reduce the prescription of unnecessary antibiotics.[2]

REVIEW METHODS

A systematic search was done until April 10, 2023, using Medline, CENTRAL and Google Scholar with combined MeSH and free text search using the terms urinalysis, urine dipstick, acute complicated pyelonephritis, and urinary tract infection.

Clinicaltrials.gov, Chinese and EU clinical trials registry and Herdin were also looked at to identify any ongoing trials. Preprints were also searched through medrxiv, chinarxiv and biorxiv.

Studies included were those that involved adults presenting with symptoms such as fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness with or without symptoms of lower tract urinary tract infection. Outcomes included were diagnosis of acute uncomplicated pyelonephritis, resolution of symptoms, improvement of symptoms, progression of symptoms, complication, sepsis, morbidity, adverse events, antibiotic change and cost. Subgroups intended were those of normal health adults and adults with co-morbidities and/or are on maintenance medications. Search was limited to studies published in the last 10 years and to only those with available full free text and published in English. Studies that involved children, pregnant women and those with structural abnormalities or complicated UTI were excluded. Studies that involved lower urinary tract symptoms only were also excluded.

RESULTS

Characteristics of included studies

Seven (7) observational studies (5 cross-sectional studies and 2 cohort studies) involving 2,485 adult patients with signs and symptoms suggestive of a urinary tract infection were included in this review. Study settings included emergency room and out-patient or primary care clinics. Six (6) studies included both male and female patients (with one study including four pregnant patients) while one study included female patients only. However, there was no study that included patients with symptoms specifically for acute uncomplicated pyelonephritis only.

Index tests used urine dipstick and/or urine microscopy. Three (3) studies had both urine dipstick and urine microscopy,[5-7] three (3) using urine dipstick alone,[7-9] and one (1) using urine microscopy.[4] Four (4) studies used urine dipsticks that were interpreted via direct visual inspection and comparison,[5,7-10] while two (2) studies used automated urine analyzers for the chemical examination.[6,9]

Reference standard used for the diagnosis of a urinary tract infection was the presence of a single organism with at least 10^5 colony forming units per milliliter in four (4) studies,[6-8, 10] while one used a reference range of 10^4 cfu/ml,[5] and another with 103 cfu/ml.[9] All studies compared the results of the index tests (urine dipstick and/or microscopy) to the urine culture results to diagnose UTI. The study of Middlekoop however also diagnosed patients to have UTI using clinical signs and symptoms, successful treatment without other focus and conclusion of the attending physician apart from a positive urine culture result.

The characteristics of the included studies are further described in Appendix 5, Appendix Table 5.2.

Diagnostic accuracy of urine dipstick – nitrites

Pooled analysis of four studies showed that the presence of nitrites on urine dipstick had a sensitivity of 0.36 (95% CI 0.25,0.49) and a specificity of 0.95 (95% CI 0.92,0.97) with the reference standard as the presence of $>10^5$ cfu/ml of a single organism in

urine culture. Other included studies showed a sensitivity of 0.7 and 0.46 and a specificity of 0.57 and 0.90 when compared to a positive urine culture with lower cut-offs at >10^4 cfu/ml and >10^3 cfu/ml respectively. See Table 2.1.

Table 2.1. Sensitivity and specificity of using urine dipstick – nitrites.

REFERENCE STANDARD	NO. OF STUDIES	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	CERTAINTY OF EVIDENCE
Urine culture >10^5 cfu/ml	4 (n=1,272)	0.36 (0.25,0.49)	0.95 (0.92,0.97)	Low
Urine culture >10^4 cfu/ml	1 (n=149)	0.70 (0.58, 0.81)	0.58 (0.46, 0.68)	Very Low
Urine culture >10^3 cfu/ml	1 (n=500)	0.46 (0.28,0.48)	0.90 (0.64, 0.99)	Moderate

The probability of a diagnosis of UTI in patients presenting with fever or flank pain increases to 92% and 88% respectively with a positive nitrite result on urine dipstick from a previous probability of 62 and 51 respectively. Meanwhile, a negative result decreases the probability to 53 and 47 percent. The presence of at least two symptoms, particularly fever and flank pain increased the probability to 90% while both fever and dysuria and fever and chills, with a positive nitrite test increased the probability 94%. See Table 2.2.

Table 2.2. Pre- and posttest probabilities using urine dipstick – nitrites as diagnostic in patients with symptoms.

SYMPTOM	REFERENCE STANDARD	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR NITRITES	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR NITRITES
Fever	Urine culture >10^5 cfu/ml	62	92	53
	Urine culture >10^4 cfu/ml	62	73	47
	Urine culture >10^3 cfu/ml	62	50	88
Flank pain	Urine culture >10^5 cfu/ml	51	88	41
	Urine culture >10^4 cfu/ml	51	35	63
	Urine culture >10^3 cfu/ml	51	83	38
Chills	Urine culture >10^5 cfu/ml	62	92	53
	Urine culture >10^4 cfu/ml	62	73	47
	Urine culture >10^3 cfu/ml	62	50	88
Fever and Flank Pain	Urine culture >10^5 cfu/ml	56	90	46
	Urine culture >10^4 cfu/ml	56	67	40
	Urine culture >10^3 cfu/ml	56	85	43
Fever and Dysuria	Urine culture >10^5 cfu/ml	67	94	58
	Urine culture >10^4 cfu/ml	67	77	52

	Urine culture $>10^3$ cfu/ml	67	55	90
Fever and Chills	Urine culture $>10^5$ cfu/ml	67	94	58
	Urine culture $>10^4$ cfu/ml	67	77	52
	Urine culture $>10^3$ cfu/ml	67	55	90

[a]Pre test probabilities computed from data from the studies of Giesen and Tan [2,4]

Diagnostic accuracy of urine dipstick – leukocyte esterase

Pooled analysis of four studies showed that the presence of leukocyte esterase on urine dipstick had a sensitivity of 0.85 (95% CI 0.0.71,0.93) and a specificity of 0.69 (95% CI 0.41,0.87) with the reference standard as the presence of $>10^5$ cfu/ml of a single organism in urine culture. Other included studies showed a sensitivity of 0.87 and 0.81 and a specificity of 0.25 and 0.58 when compared to a positive urine culture with lower cut-offs at $>10^4$ cfu/ml and $>10^3$ cfu/ml respectively. See Table 2.3.

Table 2.3. Sensitivity and specificity of using urine dipstick – leukocyte esterase.

REFERENCE STANDARD	NO. OF STUDIES	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	CERTAINTY OF EVIDENCE
Urine culture $>10^5$ cfu/ml	4 (n=1,272)	0.85 (0.71,0.93)	0.69 (0.41,0.87)	Low
Urine culture $>10^4$ cfu/ml	1 (n=149)	0.87 (0.77,0.95)	0.25 (0.15, 0.34)	Very Low
Urine culture $>10^3$ cfu/ml	1 (n=500)	0.81 (0.59, 0.89)	0.58 (0.64, 0.95)	Moderate

The probability of a diagnosis of UTI in patients presenting with fever, flank pain or chills increases to 82%, 74% or 82% respectively with a positive leukocyte esterase on urine dipstick, showing lower probabilities compared to a positive nitrite test. The presence of at least two symptoms, particularly fever and flank pain increased the probability to 78% while both fever and dysuria and fever and chills, with a positive leukocyte esterase test increased the probability 85%. On the other hand, the probability of a diagnosis of UTI in patients presenting with fever, flank pain or chills is only 26% and 18% with a negative leukocyte esterase on urine dipstick. See Table 2.4.

Table 2.4. Pre- and posttest probabilities using urine dipstick – leukocyte esterase as diagnostic in patients with symptoms.

SYMPTOM	REFERENCE STANDARD	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR LEUKOCYTE ESTERASE	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR LEUKOCYTE ESTERASE
Fever	Urine culture $>10^5$ cfu/ml	62	82	26
	Urine culture $>10^4$ cfu/ml	62	66	46
	Urine culture $>10^3$ cfu/ml	62	76	35
Flank pain	Urine culture $>10^5$ cfu/ml	51	74	18
	Urine culture $>10^4$ cfu/ml	51	54	35

	Urine culture $>10^3$ cfu/ml	51	66	25
Chills	Urine culture $>10^5$ cfu/ml	62	82	26
	Urine culture $>10^4$ cfu/ml	62	66	46
	Urine culture $>10^3$ cfu/ml	62	76	35
Fever and Flank Pain	Urine culture $>10^5$ cfu/ml	56	78	22
	Urine culture $>10^4$ cfu/ml	56	60	40
	Urine culture $>10^3$ cfu/ml	56	71	29
Fever and Dysuria	Urine culture $>10^5$ cfu/ml	67	85	31
	Urine culture $>10^4$ cfu/ml	67	70	51
	Urine culture $>10^3$ cfu/ml	67	80	40
Fever and Chills	Urine culture $>10^5$ cfu/ml	67	85	31
	Urine culture $>10^4$ cfu/ml	67	70	51
	Urine culture $>10^3$ cfu/ml	67	80	40

[a]Pre test probabilities computed from data from the studies of Giesen and Tan[2,4]

Diagnostic accuracy of urine microscopy – leukocytes and bacteria

The study by Tan (n= 451) described the performance characteristics of the presence of WBCs and bacteria to diagnose UTI. WBC $\geq$ 5/hpf had a sensitivity of 0.99 and specificity of 0.22 while a WBC count of $\geq$10/hpf and $\geq$ 20/hpf showed a sensitivity of 0.98 and 0.94 and specificity of 0.38 and 0.49 respectively. Bacterial counts of $\geq$ +1 and +2 had a sensitivity of 0.28 and 0.11 and specificity of 0.95 and 0.99 respectively.

The study by Chalmers (n=247) showed that using microscopy as a point of care test with results of a WBC $\geq$10/hpf, bacteria $\geq$ 1/hpf and epithelial cells of <5/hpf had a sensitivity of 0.57 and specificity of 0.89. The study of Middlekoop (n=381) showed a sensitivity of 0.82 and specificity of 0.59 for the presence of few to many leukocytes on gram stain. They also showed a sensitivity of 0.86 and specificity of 0.70 for presence of few to many bacteria on gram stain as well.

Using the study of Tan, the calculated pre and posttest probabilities according to symptom presentation is shown at Table 2.5 and 2.6:

Table 2.5. Pre- and posttest probabilities using WBC as diagnostic in patients with symptoms.

SYMPTOM	REFERENCE STANDARD	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR WBC	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR WBC
Fever	WBC $\geq$ 5/hpf	62	67	7
	WBC $\geq$ 10/hpf	62	72	8
	WBC $\geq$ 20/hpf	62	75	17
Flank pain	WBC $\geq$ 5/hpf	51	57	4

	WBC ≥ 10/hpf	51	62	5
	WBC ≥ 20/hpf	51	65	11
Chills	WBC ≥ 5/hpf	62	68	7
	WBC ≥ 10/hpf	62	72	8
	WBC ≥ 20/hpf	62	75	17
Fever and Flank Pain	WBC ≥ 5/hpf	56	62	5
	WBC ≥ 10/hpf	56	67	6
	WBC ≥ 20/hpf	56	70	13
Fever and Dysuria	WBC ≥ 5/hpf	67	72	8
	WBC ≥ 10/hpf	67	76	10
	WBC ≥ 20/hpf	67	79	20
Fever and Chills	WBC ≥ 5/hpf	67	72	8
	WBC ≥ 10/hpf	67	76	10
	WBC ≥ 20/hpf	67	79	20

[a]Pre test probabilities computed from data from the studies of Giesen and Tan[2,4]

Table 2.6. Pre- and posttest probabilities using bacteria as diagnostic in patients with symptoms.

SYMPTOM	REFERENCE STANDARD	PROBABILITY OF UTI BEFORE TESTING (%)[a]	PROBABILITY OF UTI AFTER TESTING POSITIVE FOR BACTERIA	PROBABILITY OF UTI AFTER TESTING NEGATIVE FOR BACTERIA
Fever	Bacteria ≥ +1	62	90	56
	Bacteria ≥ +2	62	95	60
Flank pain	Bacteria ≥ +1	51	85	44
	Bacteria ≥ +2	51	92	48
Chills	Bacteria ≥ +1	62	90	56
	Bacteria ≥ +2	62	95	59
Fever and Flank Pain	Bacteria ≥ +1	56	88	49
	Bacteria ≥ +2	56	93	53
Fever and Dysuria	Bacteria ≥ +1	67	92	61
	Bacteria ≥ +2	67	96	65
Fever and Chills	Bacteria ≥ +1	67	92	61
	Bacteria ≥ +2	67	96	65

[a]Pre test probabilities computed from data from the studies of Giesen and Tan[2,4]

The probability of a diagnosis of UTI in patients presenting with fever or chills increases to 75% if there are more than 20 WBCs seen per high power field (hpf) and increases to only 65% in patients presenting with flank pain. The presence of at least two symptoms such as fever and chills or fever and dysuria increase the probability to 79%.

In contrast, patients who present with fever or chills and have at least +2 bacteria seen on urine microscopy increases the probability of a diagnosis of UTI to 95%. Patients who present with flank pain and bacteria of at least +2 increases the probability of UTI to 92%. The presence of at least two symptoms such as fever and chills or fever and dysuria increase the probability to 96%.

CERTAINTY OF EVIDENCE

Most of the studies had a low to unclear risk of bias, mostly in the process of patient selection as not all studies indicated consecutive sampling. All index tests were performed without knowledge of the results from the reference standard, however in the studies using the urine dipsticks via direct visual interpretation/inspection,

examiners were aware of the symptoms of the patients. Risk of bias is high for the study Middlekoop as part of their reference standard included clinical assessment only to diagnose UTI regardless of urine culture result. Since the definition of AUP involves non-pregnant women only, there is high concern regarding serious indirectness as the population of the studies included both male and female adults and 2 studies used a different cut-off for its reference standard. Only one study (Tan) included female patients only. Thus, the overall certainty of evidence is low. Studies were also downgraded for indirectness due to mix population of male and female patients, use of only one component of a urinalysis and inclusion of patients with lower tract symptoms only.

RECOMMENDATIONS FROM OTHER GROUPS

Table 2.7. Summary recommendation from groups and agencies.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013	Urinalysis and Gram stain are recommended.	Strong recommendation, Moderate quality of evidence
European Association of Urology 2022	Perform urinalysis, including the assessment of white and red blood cells and nitrite for routine diagnosis	Strong
Asian Association of UTI and STI 2022	Urinalysis, including the assessment of white and red blood cells and nitrites is recommended for routine diagnosis	Grade C

ONGOING STUDIES AND RESEARCH GAPS

There were no ongoing studies looking at utility of the use of a urinalysis in decreasing risks for sepsis, mortality, and its impact on the prognosis for adult patients with acute uncomplicated pyelonephritis. Studies on the sensitivity of a symptom-based strategy in comparison with a urinalysis as a diagnostic tool may be of benefit to identifying patients needing empiric antibiotic therapy in the primary care setting. Local studies to evaluate the diagnostic utility and cost effectiveness of using a urine dipstick for primary care clinics that have limited access to laboratories should be conducted.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

There were no local cost effectiveness studies on the use of urinalysis to diagnose acute uncomplicated pyelonephritis in adults. A urinalysis costs P40 in government hospitals and from Php 300-400 in private hospitals and diagnostic centers.[11] Ten in 1 urine dipsticks cost approximately Php 500-600 for 100 pieces.

A cost effectiveness study done in the Netherlands concluded that the use of a urine dipstick and performing a good history (costs 10-17 euros) was the most cost-effective strategy to diagnose UTI.[12]

Patient's values and preference, equity, acceptability, and feasibility

There were no local studies found that investigated patient's values, preferences, equity, acceptability, and feasibility on the use of urinalysis among symptomatic adults to diagnose acute uncomplicated pyelonephritis.

REFERENCES

1. Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults. Philippines: Philippine Society of Microbiology and Infectious Diseases [Updated 2013]. Available from: https://www.psmid.org/diagnosis-and-management-of-urinary-tract-infections-in-adults-2013-update-part-1/
2. Giesen, LGM. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Family Practice 2010; 11(78); https://doi.org/10.1186/1471-2296-11-78
3. Plana, M.N., Arevalo-Rodriguez, I., Fernández-García, S. et al. Meta-DiSc 2.0: a web application for meta-analysis of diagnostic test accuracy data. BMC Med Res Methodol 22, 306 (2022). https://doi.org/10.1186/s12874-022-01788-2
4. Tan, NCT. Accuracy of urinary symptoms and urine microscopy in diagnosis urinary tract infection in women. Oxford Family Practice 2018; 20 (20) 1-8 doi:10.1093/fampra/cmy108
5. Bafna P et al. Reevaluating the true diagnostic accuracy of dipstick tests to diagnose urinary tract infection using Bayesian latent class analysis. PLoS ONE 2020 15(12):e0244870 https://doi.org/10.1371/journal.pone.0244870
6. Middelkoop SJM, et al, Routine tests and automated urinalysis in patients with suspected urinary tract infection at the ED, American Journal of Emergency Medicine 2016, http://dx.doi.org/10.1016/j.ajem.2016.05.005
7. Chalmers, L., et al. The role of point of care tests in antibiotic stewardship for urinary tract infections in a resource-limited setting on the Thailand-Myanmar border . Tropical Medicine and International Health 2015 20(10:1281-12899 doi:10.1111/tmi.12541
8. Bellazreg, F., et al. Diagnostic value of dipstick test in adult symptomatic urinary tract infections: results of a cross-sectional Tunisian study. Pan African Medical Journal 2018; 33 (131) doi:10.11604/pamj.2019.33.131.17190
9. Chernaya, A. et al. Validity of the urinary dipstick test in the diagnosis of urinary tract infections in adults. Danish Medical Journal 2022; 69(1):A07210607
10. Prah, JK., etal. Evaluation of urinalysis parameters and antimicrobial susceptibility of uropathogens among out-patients at University of Cape Coast Hospital 2019; 53 (1):44-51
11. Del Rio, Y. Urinalysis Test Prince in the Philippines 2023: What It is For?. Medical Trends Now website https://medicaltrendsnow.com/urology/urinalysis-test-price-in-the-philippines/#Urinalysis_Test_Price_in_the_Philippines_How_Much_and_Where_to_Get_Tested
12. Bosmans, JE, Coupe, VMH, et. al. Cost-effectiveness of different strategies for diagnosis of uncomplicated urinary tract infections in women presenting in primary care. PlosOne 2017; 12(11): e0188818

Question 3. Among symptomatic children*, should we recommend urinalysis to confirm the diagnosis of urinary tract infection prior to initiation of treatment?

***Fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness with or without symptoms of lower urinary tract infection**

Recommendations

Among symptomatic children 5 years old and younger, we **suggest** the use of urinalysis with or without leukocyte esterase and nitrites in the diagnosis of urinary tract infection prior to initiation of treatment. *(**Low certainty of evidence, Weak recommendation**)*

Consensus Issues

- The panel highlighted that pediatric patients with fever but have no focus symptoms and unknown source of infection are better suited to be tested with urinalysis to help rule in or rule out UTI.
- While it is suggested to use urinalysis as a modality for diagnosing UTI, it was also noted by the panel that it has a high rate of false positivity, thus it is better to interpret results with clinical guidance or have a urine culture as to be more confident in diagnosing UTI in children.
- Although it is optimal to test with leukocyte esterase and nitrite if available, the panel specified that a negative nitrite and leukocyte esterase tests does not necessarily mean the patient has no UTI. The panel detailed that nitrites are produced by Enterobacteriaceae and will be negative if the specific bacteria is not present, while leukocyte esterase might be affected if with short contact time with the urinary bladder.

Recommendations

Among symptomatic children above 5 years old, we **suggest** the use of urinalysis with or without leukocyte esterase and nitrites in the diagnosis of Urinary Tract Infection prior to initiation of treatment. *(**Very Low certainty of evidence, Weak recommendation**)*

Consensus Issues

- Although the evidence of the study focuses on 5 years old and younger, the panel did not find the indirectness as a reason not to agree to such a recommendation.

KEY FINDINGS

This review found evidence that urine test using the clean-catch method outperformed clinicians' judgment in estimating the likelihood of a UTI on urine culture among children less than 5 years of age. Costs were also marginally better compared to clinical judgement alone both in the short term and long term. There was no difference between the incidence of recurrent UTI and the risk for end stage renal disease among those who were diagnosed using clinical judgment alone or those who had their urine tested.

INTRODUCTION

Urinary tract infection (UTI) remains to be one of the most common causes of bacterial infections in childhood. It is estimated that within the first year of life, 3.7% of boys are affected compared to only 2% in girls. After infancy, UTI significantly becomes more prevalent in girls and during prepubertal age, 3% of girls contract UTI - compared to only 1% in boys.[1-3]

Prompt diagnosis and treatment of UTI are important for the prevention of acute complications as well as renal scarring. In the study of Mattoo et.al, they noted that the prevalence of renal scarring after febrile UTI is at 15-39%, though in majority of children development of renal scarring may not be clinically significant.[8-11] Delayed initiation of antibiotic treatment is associated with increased risk of scarring, with the odds of new renal scarring at 74% - which is lower among children whose treatment started within 24 hours of onset of fever, compared with those whose treatment started after 72 hours of fever.[12]

In accurate diagnosis of UTI, a targeted history and physical examination and positive urinary findings are essential. Unfortunately, fever may be the only symptom. In current practices, antibiotics should be started within 48 hours of fever onset because delayed treatment increases the risk of renal scarring.[12-14] Unfortunately this led to injudicious use of antibiotics among pediatric UTI, and antibiotic resistance of pathogens causing UTI at any age is a growing concern internationally.[15-19] Hence, it is prudent to determine if the child really has UTI and to choose an antimicrobial to which only a small proportion of organisms are resistant.

Urine culture, the gold standard for diagnostic evaluation of UTI, unfortunately takes 1-2 days before results become available, hence urinalysis is often used as a substitute diagnostic aid prior to antibiotic treatment of UTI.[20] There are different urine tests available locally. The most common urine tests utilized in the diagnosis of UTI are urine dipstick, microscopy, and combination of both (routine urinalysis). In the clinical practice guideline released by AAP last 2011, the sensitivity of urine dipstick test using leukocyte esterase test alone is at 83% with range of 67-94% compared to nitrite esterase test at 53% with range of 15-82%. The low sensitivity of nitrite test mostly observed among infants were due to short dwell time (<4 hours) of urine in the bladder, and less time for conversion of nitrate to nitrite to occur. When tests were combined, sensitivity increased to 93% with range of 90-100%. In contrast, microscopy of WBC and bacteria has a sensitivity of 73% and 81%, respectively. If urine dipstick and microscopy is combined like in routine urinalysis, the sensitivity increases to 99.8% with range of 99 to 100%.[21]

This review intends to determine the need for urinalysis prior to treatment of Pediatric urinary tract infection to aid in diagnosis, improve clinical outcomes, and to prevent complications and antimicrobial resistance.

REVIEW METHODS

A comprehensive systematic search of related literature was performed from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics, CENTRAL and NICE UTI guideline, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. The search was

conducted using the following terms: symptomatic UTI, urinalysis vs none, clinical manifestation, diagnosis, acute uncomplicated pyelonephritis, resolution of symptoms, improvement, progression, complication, sepsis, morbidity, adverse events, antibiotic change, and cost.

For this review, the PICO was as follows: Population – symptomatic children presenting with fever, chills, vomiting, diarrhea, flank pain, costovertebral angle tenderness with or without symptoms of lower urinary tract infection; Intervention - urinalysis; Control - no test/ clinical presentation only; Outcome - diagnosis of UTI, cost and incidence of recurrent UTI and end stage renal disease. Randomized controlled trials, observational studies, systematic reviews, and meta-analyses were also searched.

RESULTS

Characteristics of included studies

One large prospective cohort [22] was included in this review. The study of Hay et al. compared the use of signs and symptoms alone versus signs and symptoms with urine dipstick in the diagnosis of urine culture-based UTI among children less than 5 years of age. It also performed health economic analysis between the two groups, as well as incidence of recurrent UTI and end stage renal disease.

No study was found that compared clinical judgment with diagnostic test among the 6–18-year-old age group.

Efficacy outcomes

The study of Hay et al reported that Urine dipstick using the clean-catch method outperformed clinicians' judgment in estimating the likelihood of a UTI on urine culture, with an OR of 2.53 (95% CI 1.46, 4.40). The diagnostic utility of clinical judgment with urine sampling had an area under the receiver operating characteristic (AUROC) adjusted OR at 0.933 (95% CI 0.9,0.97) which is higher compared to clinical judgment alone, (AUROC Adjusted OR 0.899 (95% CI 0.85,0.95). The increase in the AUROC while using the symptoms, signs and urinalysis was around 0.06. The validated AUROC for the symptoms and signs model 0.876 demonstrated a very good accuracy but adding urinalysis increased validated AUROC to 0.903 (p value 0.009), suggesting very strong evidence that the urine dipstick increase the AUROC when added to the symptoms and signs model. A sensitivity specificity analysis was also performed which showed that compared to urine culture, clinical judgment has a sensitivity of 0.47 with 95% CI of 0.34, 0.60 and specificity of 0.95 with 95% CI of 0.94, 0.96. On the other hand, urine dipstick has a sensitivity of 0.34 with 95% CI 0.26, 0.43 and a specificity of 0.98 with 95% CI of 0.98, 0.99. Showing that clinical judgment has a slightly higher sensitivity in diagnosing Pediatric UTI but urine dipstick has more superior specificity. Urine dipstick exhibited a higher positive predictive value at 33.6% compared to Clinical judgement at 16.7%, showing that more patients who tested positive from the dip stick have UTI.

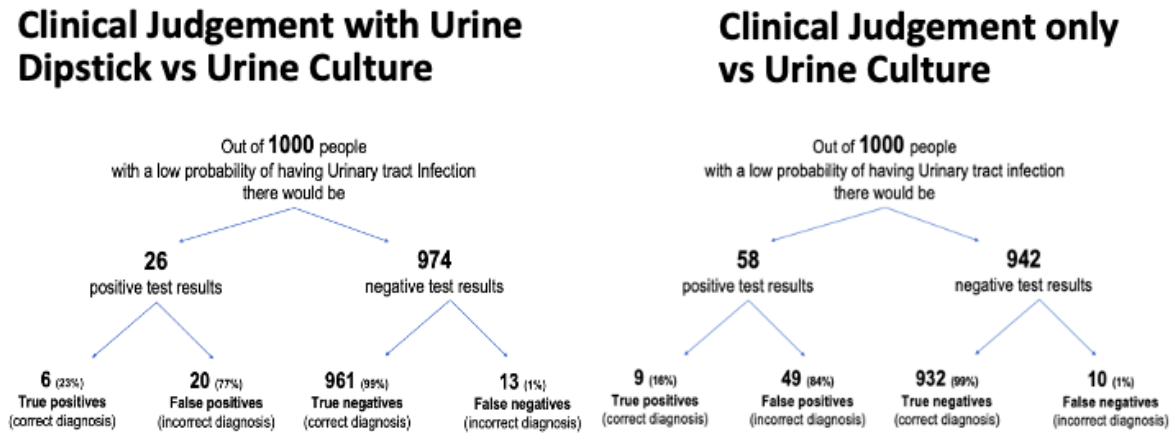

Figure 3.1. Efficacy outcome comparison between clinical judgment with urine dipstick vs clinical judgment alone.

The study showed no significant difference in the risk for recurrent UTI and end stage renal disease (ESRD) among those treated with antibiotics based on clinical judgment alone and those based on conservative urine sampling. The average number of UTI per 10,000 patients at 3 years was 171 for clinical judgment alone, and 170.99 for conservative urine sampling with an OR of 0.79 and CI of 0.79, 1.25. The risk for ESRD was 0.288, equal for clinical judgment alone and for conservative urine sampling.

Table 3.1. GRADE summary of findings table comparing studies for urine test vs no urine test in diagnosing pediatric urinary tract infection.

CRITICAL OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Chances of Correct Diagnosis	1 observational study (n=7,163)	OR 2.53	1.46, 4.40	Benefit	Low
Health Economic cost	1 observational study (n=7,163)	SMD 0.74	0.72, 0.76	Equivalent	Low
Average lifetime cost	1 observational study (n=7,163)	SMD 2.24	2.22, 2.26	Inconclusive	Low
UTI at 3 years per 10,000 patients	1 observational study (n=7,163)	OR 0.99	0.81, 1.21	Inconclusive	Low
Risk for ESRD	1 observational study (n=7,163)	SMD 0	-0.26, 0.26	Equivalent	Low

CERTAINTY OF EVIDENCE

The overall certainty was low for each of the outcomes: diagnosis of UTI, cost and incidence of recurrent UTI and end stage renal disease. Downgrading was done

because the Hay study is only an observational study, follow up was incomplete and due to indirectness wherein they used urine dipstick alone instead of urinalysis.

RECOMMENDATIONS FROM OTHER GROUPS

Table 3.2. Summary of recommendations from other groups and agencies.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
National Institute for Health and Care Excellence (NICE) 2007 [2023] (accessed January 5, 2023)	Emphasized the importance of prompt, microbiologically confirmed diagnosis and treatment of children, particularly in primary care where there is evidence that UTIs are missed. Suggests that clinicians should test for UTI in children < 5 years with unexplained fever, vomiting, lethargy, irritability, poor feeding, abdominal pain, offensive urine, hematuria, frequency or dysuria.	Not reported
American Academy of Pediatrics: Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months, 2011 [2021] (accessed January 5, 2023)	To establish the diagnosis of UTI, clinicians should require *both* urinalysis results that suggest infection (pyuria and/or bacteriuria) *and* the presence of at least 50 000 colony-forming units (CFUs) per mL of a uropathogen cultured from a urine specimen obtained through catheterization or SPA.	Recommendation/ Insufficient evidence

ONGOING STUDIES AND RESEARCH GAPS

As of January 12, 2023, there were no ongoing trials investigating whether clinical judgement vs clinical judgement with urinalysis is more useful in correctly diagnosing urinary tract infection in children.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

Hay et.al also determined the health economic analyses that showed that clinical assessment with urine dipstick would result into fewer urine sampling. Costs and patient outcomes were marginally better with clinical assessment with urine dipstick compared to clinical judgement alone both in short term; with net monetary benefit for clinical judgment at £1089 (Php 73,115.46) vs conservative urine sampling at £1090.44 (Php 73,182.6) and an incremental net monetary benefit of 0.74 (95% CI 0.72,0.76) and long term; with average lifetime cost of UTI for clinical judgement alone at £200.16 (Php 13,438) compared to conservative urine testing at £197.92 (Php 13,228.35) with net incremental monetary benefit of £2.24 (Php 150.40) (95% CI 2.22-2.26). Implying that use of urine testing incurred less cost compared to clinical judgement due to judicious use of antibiotics.[22]

On one hand, short term non-monetary benefit for UTI not needing antibiotics was £1091.43 (Php 73,249.74) for clinical judgement compared to £1090.86 (Php 73,240.34) for with conservative urine sampling. On the other hand, UTI necessitating use of antibiotics incurred a short term non-monetary benefit of £1091.45 (Php 73,279.95) for clinical judgement and £1090.90 (Php 73,243.03) for with conservative urine sampling. Implying that short term monetary benefit is almost the same, with slightly less cost among those with urine testing.[23]

The average urinalysis cost in government hospitals ranges from Php 40 to100; in private hospitals it ranges from Php 470 to 890 and in clinics the average cost is at Php 75.[24]

There was no local cost effectiveness study regarding use of urinalysis for pediatric UTI identified.

Patient's values and preference, equity, acceptability, and feasibility

There was also no study found among Filipino patients' values, preference, equity, feasibility, and acceptability on the use of urinalysis for diagnosing UTI in children.

REFERENCES

1. Zorc JJ , Levine DA , Platt SL , et al.; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics . Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics. 2005;116(3):644–648
2. Shaikh N , Morone NE , Bost JE , Farrell MH . Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008;27(4):302–308
3. Kanellopoulos TA , Salakos C , Spiliopoulou I , Ellina A , Nikolakopoulou NM , Papanastasiou DA . First urinary tract infection in neonates, infants and young children: a comparative study. Pediatr Nephrol. 2006;21(8):1131–1137
4. Akram M , Shahid M , Khan AU . Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in J N M C Hospital Aligarh, India. Ann Clin Microbiol Antimicrob. 2007;6:4
5. Chakupurakal R , Ahmed M , Sobithadevi DN , Chinnappan S , Reynolds T . Urinary tract pathogens and resistance pattern. J Clin Pathol. 2010;63(7):652–654
6. Lutter SA , Currie ML , Mitz LB , Greenbaum LA . Antibiotic resistance patterns in children hospitalized for urinary tract infections. Arch Pediatr Adolesc Med. 2005;159(10):924–928
7. Department of Health-Research Institute for Tropical Medicine. Bacteriology and Antibiogram of Urinary Tract Infection in the Philippines from 2017-2021. Antimicrobial Resistance and Surveillance. February 6, 2023.
8. Wennerström M , Hansson S , Jodal U , Sixt R , Stokland E . Renal function 16 to 26 years after the first urinary tract infection in childhood. Arch Pediatr Adolesc Med. 2000;154(4):339–345
9. Salo J , Ikäheimo R , Tapiainen T , Uhari M . Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics. 2011;128(5):840–847
10. Wennerström M , Hansson S , Hedner T , Himmelmann A , Jodal U . Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. J Hypertens. 2000;18(4):485–491
11. Mattoo TK . Vesicoureteral reflux and reflux nephropathy. Adv Chronic Kidney Dis. 2011;18(5):348–354
12. Shaikh N , Mattoo TK , Keren R , et al . Early antibiotic treatment for pediatric febrile urinary tract infection and renal scarring. JAMA Pediatr. 2016;170(9):848–854
13. Karavanaki KA , Soldatou A , Koufadaki AM , Tsentidis C , Haliotis FA , Stefanidis CJ . Delayed treatment of the first febrile urinary tract infection in early childhood increased the risk of renal scarring. Acta Paediatr. 2017;106(1):149–154
14. Oh MM , Kim JW , Park MG , Kim JJ , Yoo KH , Moon G . The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. Eur J Pediatr. 2012;171(3):565–570

15. Edlin RS , Shapiro DJ , Hersh AL , Copp HL . Antibiotic resistance patterns of outpatient pediatric urinary tract infections. J Urol. 2013;190(1):222–227
16. Zorc JJ , Kiddoo DA , Shaw KN . Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev. 2005;18(2):417–422
17. Doi Y , Park YS , Rivera JI , et al . Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis. 2013;56(5):641–648
18. Zhu FH , Rodado MP , Asmar BI , Salimnia H , Thomas R , Abdel-Haq N . Risk factors for community acquired urinary tract infections caused by extended spectrum β-lactamase (ESBL) producing Escherichia coli in children: a case control study. Infect Dis (Lond). 2019;51(11–12):802–809
19. Frazee BW , Trivedi T , Montgomery M , Petrovic DF , Yamaji R , Riley L . Emergency department urinary tract infections caused by extended-spectrum β-Lactamase-producing nterobacteriaceae: many patients have no identifiable risk factor and discordant empiric therapy is common. Ann Emerg Med. 2018;72(4):449–456
20. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128(3):595–610.
21. American Academy of pediatrics. CLINICAL PRACTICE GUIDELINE Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months. PEDIATRICS Volume 128, Number 3. 2011. doi:10.1542/peds.2011-1330
22. Hay AD, Birnie K, Busby J, et al.; on behalf of the DUTY team. The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness. Southampton (UK): NIHR Journals Library; 2016 Jul. (Health Technology Assessment, No. 20.51.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK373510/ doi: 10.3310/hta20510
23. National Institute for Health and Care Excellence. Urinary Tract Infection in Children: Diagnosis,Treatment and Long Term Management. London: NICE; 2007.
24. https://medicaltrendsnow.com/urology/urinalysis-test-price-in-the-philippines/#:~:text=The%20urinalysis%20test%20price%20in%20the%20Philippines%20is%20between%20PHP,depending%20on%20the%20test%20services. Accessed: January 12, 2023 11pm.

Antibiotic Management of UTI

Question 4. Among adult patients diagnosed with Acute Uncomplicated Cystitis (AUC), should we recommend antibiotics for treatment?

Recommendations

Among adult patient diagnosed with acute uncomplicated cystitis, we suggest the use of the following oral antibiotics:

- Fosfomycin
- Nitrofurantoin
- Alternative:
    - Cephalosporin – 2nd and 3rd generation
    - Co-amoxiclav
    - Trimethoprim-sulfamethoxazole* (TMP-SMX)

*(**Low certainty of evidence, Weak recommendation**)*

**If culture show susceptibility*

Footnote:

- *Some suggested dose and duration of antibiotics for treatment of adult AUC are as follows:*
    - *Fosfomycin trometamol 3g single dose per orem (PO).*
    - *Nitrofurantoin macrocrystals 100mg QID for 5 days PO.*
    - *Cefuroxime 250mg to 500mg BID for 7 days PO.*
    - *Cefaclor 500mg TID for 7 days PO.*
    - *Cefixime 200mg BID for 7 days PO.*
    - *Cefpodoxime proxetil 100 mg BID for 7 days PO.*
    - *Ceftibuten 200mg BID for 7 days PO.*
    - *Co-amoxiclav 625mg BID to TID for 7 days PO.*
    - *TMP-SMX 160/800 ng BID for 3 days PO.*
- *Review local and institutional antibiograms, if available.*
- *Adjust dose depending on GFR.*

Consensus Issues

- The panel decided on the antibiotics on the treatment of AUC, based on the Annual Resistance Surveillance Program (ARSP) annual report of 2021.
- The panel advocated that healthcare providers must follow evidence-based guidelines for prescribing antibiotics, ensuring accurate diagnosis, considering treatment risks and benefits, and promoting alternative strategies. The panel highlighted that public health efforts and prescribed courses are crucial for reducing antibiotic resistance and minimizing side effects.
- To treat acute uncomplicated cystitis, control infection, relieve symptoms and shorten the length of the illness, the panel emphasized that antibiotics are crucial. To ensure an accurate diagnosis and effective treatment, caution should be exercised when using any medication.
- The panel noted that the benefits of antibiotic treatment frequently outweigh concerns; to reduce potential risks, use antibiotics sparingly.
- The panel pointed out that cost can be moderate to expensive specially if AUC is recurrent.

KEY FINDINGS

This review included nine randomized control trials that determined whether treatment of antibiotics is superior compared to placebo in the treatment of Acute uncomplicated cystitis in adult patients.

Nine randomized control studies showed marked clinical improvement and microbiologic success among those treated with antibiotics compared to those given only placebo. On one hand, there was also less persistence of symptoms by day 3, less recurrence of UTI and lesser development of complications such as pyelonephritis among those treated with antibiotics compared to placebo or symptomatic management. On the other hand, there were more reported adverse events such as gastrointestinal among those given antibiotics.

The overall certainty was low for each of the outcomes: clinical improvement and recurrence of UTI due to serious risk of bias due to lack of mention of concealment allocation and high attrition rate, imprecision, and inconsistencies.

INTRODUCTION

It is estimated that one-third of women under the age of 24 will experience at least one episode of a urinary tract infection (UTI) requiring antibiotic treatment.[7] Although frequently self-limiting,[7-11] standard antimicrobial treatment may still fail. AUC is prone to recur, needing several courses of antibiotics per year. AUC accounts for a considerable proportion of antibiotic prescriptions.[12] Overuse of antibiotics leads to the selection of resistant strains and contributes to the frequent development of side effects of antibiotic therapy.[13-15]

Antibiotic therapy is standard treatment for AUC definite benefits are few and often can lead to marked, harmful antibiotic overtreatment. Usually, bacteriuria and AUC specific symptoms disappear spontaneously.[16] Due to rising issues regarding antibiotic prescriptions' costs, side effects, and rates of resistance as well as current practice, where women with uncomplicated UTI are willing to delay or decline antibiotics due to fear of possible side effects,[11, 17-18] studies for alternative treatment strategies for women with uncomplicated UTIs are needed.

REVIEW METHODS

A comprehensive systematic search of related literature was performed from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and NICE UTI guideline, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. Search was conducted using the following terms: symptomatic UTI, urinalysis vs none, clinical manifestation, diagnosis, acute uncomplicated pyelonephritis, resolution of symptoms, improvement, progression, complication, sepsis, morbidity, adverse events, antibiotic change, and cost.

For this question, the PICO was as follows: Population – adult patients with AUC (normal, with comorbidities); Intervention – antibiotics (nitrofurantoin, fosfomycin, quinolones, amoxicillin, ampicillin, trimethoprim- sulfamethoxazole, beta lactams); Control - no antibiotics/Placebo; Outcome - clinical improvement, microbiologic

success, recurrence of UTI, worsening of events and adverse events. Randomized controlled trials, observational studies, systematic reviews, and meta-analyses were searched.

RESULTS

Characteristics of included studies

Nine randomized controlled trials [19,20,21,22,23,24,25,26,27] were included in this review. All the RCTs were conducted in European countries, including women aged 15-84 years. All women presented with symptoms suggestive of lower urinary tract infection. All the RCTs used antibiotics as the treatment arm, (pivmecillinam, nitrofurantoin, cefixime, cotrimoxazole ofloxacin, cotrimoxazole amoxicillin, fosfomycin, norfloxacin and ciprofloxacin). Five of the RCT used inactive agent as placebo [19,20,21,22,23], while three study used ibuprofen as placebo [24-26] and one study used diclofenac [27].

The review included 5 efficacy outcomes and 1 safety outcome. Out of these outcomes, 8 studies reported clinical improvement, 6 studies reported microbiologic success, 5 studies reported adverse events, 1 study reported recurrence of UTI, 4 studies reported persistence of symptoms and 3 studies reported development of complication.

The risk of bias for the studies included in this review are generally rated low due to lack of allocation concealment [19,21] and high attrition rate [19].

Efficacy outcomes

Eight RCTs [19,20,21,22,24,25,26,27] reported that there is a significant improvement in clinical symptoms among those treated with antibiotics compared to those only given placebo with an RR of 1.59 with 95% CI 1.47, 1.72 and a p value of <0.00001. The certainty of evidence for this outcome was rated low due to serious risk of bias from studies (19,21,22) that failed to mention allocation and concealment and one study [19] that has a high attrition rate. The studies also had a considerable inconsistency with an I^2 of 93%.

This is congruent with the pooled result of six RCTs [19-21, 25-27] which reported significant microbiologic clearance among those with culture positive UTI given with antibiotics compared to those only given placebo with an RR of 1.3 with 95% CI 1.21, 1.39 and a p value of <0.00001. The certainty of evidence for this outcome was rated moderate due to serious risk of bias from studies [19,21] that failed to mention allocation and concealment and one study [19] that has a high attrition rate.

Four RCTs [24-27] observed that more symptoms persist beyond three days of treatment among those only given with placebo with an RR 0.59 with 95% CI 0.3051, 0.67 and a p value of < 0.0004 compared to those given antibiotics. The certainty of evidence for this outcome was rated moderate due to significant heterogeneity of 79%.

Six RCTs [19-24] showed a significant number of recurrences of UTI among those only given placebo compared to those given antibiotics with an RR of 0.60 and 95% CI of 0.48, 0.76 and a p value of <0.0003. The certainty of evidence for this outcome was rated low due to serious risk of bias from studies [19,21,22,23] that failed to mention allocation concealment and one study [19] that has a high attrition rate. The studies had a considerable inconsistency with an I^2 of 78%.

Three RCTs [27,29,30] observed a reduction of cases of pyelonephritis those treated with antibiotics with an RR of 0.08 (95% CI 0.02, 0.32) with P value of 0.0004. The certainty of evidence for this outcome was rated high.

Safety outcomes

The result of five RCTs [19, 20, 22-24] showed there is a significant number of those developing adverse reactions: gastrointestinal symptoms (nausea and diarrhea) and sleep disturbance were observed among those given with antibiotics compared to those given placebo with an RR of 1.45 and 95% CI of 1.13, 1.85 and p value of 0.003. The certainty of evidence for this outcome was rated low due to serious risk of bias from studies [19,21,22,23] that failed to mention allocation and concealment and one study [19] that has a high attrition rate. There was also serious inconsistency wherein the boundaries of the confidence intervals were at the same side but one study [20] and four studies [20,22,23,24] crossed the line of no difference.

Table 4.1. Antibiotic vs placebo for treatment of acute uncomplicated cystitis

Critical OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Clinical improvement	8 RCTs (n=1,765)	RR 1.59	1.47, 1.72	Benefit	Low
Microbiologic success	6 RCTs (n=276)	RR 1.3	1.21, 1.39	Benefit	Moderate
Persistence of symptoms after D3	4 RCTs (n=517)	RR 0.59	0.51, 0.67	Benefit	Low
Recurrence of UTI	6 RCTs (n=1,327)	RR 0.60	0.48, 0.76	Benefit	Low
Development of Complication (Pyelonephritis)	3 RCTs (n=1096)	RR 0.08	0.02, 0.32	Benefit	High
Adverse events	5 RCT (n=1,552)	RR 1.45	1.13, 1.85	Harm	Moderate

CERTAINTY OF EVIDENCE

The overall certainty of evidence is graded low. Downgrading was due to serious risk of bias due to lack of mention of allocation concealment [19,21-23] and high attrition rate [19]. There were also serious issues in inconsistencies with 3 outcomes reporting considerable I^2.

RECOMMENDATIONS FROM OTHER GROUPS

Table 4.2. Summary of recommendations from other groups and agencies

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Philippine Clinical Practice Guidelines on the Diagnosis of Urinary Tract Infection in Adults 2013 Update [59]	First-line treatment for AUC: -Nitrofurantoin macrocrystals 100mg given four times a day for 5 days OR -Fosfomycin trometamol 3g taken as single dose Alternative: -Ofloxacin 200mg twice a day for 3 days -Ciprofloxacin 250mg twice a day for 3 days -Ciprofloxacin extended release 500mg once a day for 7 days -Levofloxacin 250mg once a day for 3 days -Norfloxacin 400mg twice a day for 3 days -Amoxicillin-clavulanate 625mg twice a day for 7 days -Cefuroxime 250mg twice a day for 7 days -Cefaclor 500mg three times a day for 7 days -Cefixime 200mg twice a day for 7 days -Cefpodoxime proxetil 100mg twice a day for 7 days -Ceftibuten 200mg twice a day for 3 days Only if with proven susceptibility: Trimethoprim-sulfamethoxazole 160/800mg twice a day for 3 days	Strong recommendation, High quality of evidence
National Antibiotic Guideline 2018 [1] (accessed January 18, 2023)	First-line treatment for AUC: -Nitrofurantoin macrocrystals 100 mg given four times a day for five days OR -Fosfomycin 3g/sachet dissolved in 3-4 oz (90-120 ml) of water and taken as a single dose, according to the guidelines. Alternative: -Cefuroxime 250 mg taken twice a day for 7 days -Cefixime 200 mg taken twice a day for 7 days OR -Co-amoxiclav 625 mg taken twice a day for 7 days.	not reported
Infectious Diseases Society of America (IDSA) 2010 guidelines [28] (accessed January 18, 2023)	First line medications: -Fosfomycin 3g single dose -Nitrofurantoin 100mg twice a day x 5days -Cotrimoxazole 160mg/800mg/tab twice a day for 3 days Alternative medications: -Ciprofloxacin 250mg twice a day x 3 days or 500mg once a day x 3 days -Levofloxacin 250mg once a day x 3 days	not reported

	-Ofloxacin 200mg once a day x 3 days or 400mg single dose	
Korean Association of Urogenital Tract Infection and Inflammation [29] (accessed January 18, 2023)	The CPG recommended: - 3-day fluoroquinolone therapy has been widely used and recommended as an empirical antibiotic treatment for acute cystitis -Ciprofloxacin 500 mg oral twice a day for 3 days OR Ciprofloxacin SR 500 mg once a day for 3 days -Tosufloxacin 150 mg oral twice a day	-Level of evidence: 1 RCT, Grade of recommendation: Good evidence -Level of evidence: 1 RCT, Grade of recommendation: Moderate evidence).
Hongkong's Center for Health Protection [30] (accessed January 18, 2023)	First line antibiotics used for AUC are: -Nitrofurantoin 50mg four times a day taken for 5 days -Amoxicillin 250mg/125mg three times a day or 875mg/125mg twice a day -Quinolones can also be used as an alternative antibiotic.	not reported
Centers for Disease Control and Prevention (2017) [31] (accessed January 18, 2023)	nitrofurantoin (NTF), sulfamethoxazole-trimethoprim (SMX-TMP; for which local resistance is <20%), or fosfomycin (FM) as appropriate first-line agents.	not reported
Bacteriology and Antibiogram of UTI in the Philippines from 2017-2021 [32] (DOH, RITM Antimicrobial Resistance Surveillance Reference Laboratory)	Amikacin, Nitrofurantoin, Ertapenem, Piperacillin Tazobactam, Ampicillin Sulbactam, Cefazlin, Amoxiclav, Cefuroxime, Ceftriaxone, Ciprofloxacin, Tobramycin, Cefepime, Cefoxitin, Ceftazidime, Aztreonam, Gentamicin, Tetracycline, Doripenem, Levofloxacin, Penicillin, Streptomycin, Cotrimoxazole	not reported

ONGOING STUDIES AND RESEARCH GAPS

As of January 21, 2023, there is one ongoing trial that determine whether the use of Ibuprofen is as equally effective as Mecillinam (antibiotic) in the treatment of Acute uncomplicated cystitis.[33]

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Local resistance pattern of oral antibiotics

E. coli in urine isolates appears to be most susceptible to oral nitrofurantoin (5.9%) and most resistant to oral co-trimoxazole (55.2%). Table 4.3 shows the comparison of different oral antibiotics used in AUC in adults in terms of resistance rates against *E. coli* in urine isolates of outpatients.

Table 4.3. Oral antibiotics *E. coli* resistance rate in urine isolates of out-patients (ARSP, 2021)[37]

Drugs	% Resistance
Nitrofurantoin (n=373)	5.9%
Ampicillin Sulbactam (n=165)	14.5%
Amoxicillin Clavulanic (n=616)	20.5%
Cefuroxime (n=58)	39.7%
Ciprofloxacin (n=617)	48.9%
Co-trimoxazole (n=616)	55.2%

Cost

No cost-effectiveness studies are available in the Philippines. Table 4.4 shows the variation of total cost of different oral antibiotics used in AUC in adults in based on duration of treatment and price per dose.

Table 4.4. Summary of cost of oral antibiotics

Drug	Duration	Price per Dose	Total
First Line			
Nitrofurantoin	5 days [38]	P 76 per 100 mg/cap [39]	P 760
Fosfomycin	Single dose [38]	P 512 per 3g sachet [40]	P 512
		DPRI P 412.5 per 3g sachet [41]	P 412.5
Alternative			
Cefuroxime	3-7 days [38]	P 56.5 per 250mg/cap [42]	P 113-791
		DPRI P 44 per 500mg/cap [43]	P 264-616
Cefixime	3-7 days [38]	P 90.75 per 200mg/cap [44]	P544.5-1,270.50
		DPRI P 31 per 200mg/cap [45]	P 186-434
Co-Amoxiclav	3-7 days [38]	P 41.25 per 625mg/cap [46]	P 247.50-577.50
Oral Antibiotics base on ARSP[37]			
Nitrofurantoin	Same as above		
Cefuroxime	Same as above		
Amoxicillin-Clavulanic	Same as above		
Ampicillin-Sulbactam	3-7 days [38]	P 93.68 per 375mg/cap [48]	P 1,124.16 - 2,623.04
		P 94.25-116.34 per 750mg/cap [48]	P 565.5-1,319.50 – P 698.04-1,628.76
		P 620.39 per 250mg/5mL 60ml suspension [49]	P 1,240.78-1,861.17
Ciprofloxacin	3 days [38]	P 25-48 per 500mg/cap [50]	P 150-288
		DPRI P 1.3 per 500mg/cap [51]	P 7.8
Cotrimoxazole	3 days [38]	P 90-281 per 400mg/80mg/5ml 60ml syrup [52-54]	P180-562

		P 6.5 per 400mg/80mg/tab [53-54]	P 39
		P 9-15.88 per 800mg/160mg/tab [53-54]	P 54-95.28
		DPRI P15.4 per 200mg/40mg/5ml 70ml [55]	P 46.20
		P 29.99 per 400mg/80mg/5ml 80ml suspension [56]	P 80.97
		P 0.8 per 400mg/80mg/tab [57]	P 4.8
		P 1.9 per 800mg/160mg/tab [58]	P 11.4

Patient's values and preference, equity, acceptability, and feasibility

No studies indicating patient values and preferences were found during the literature review.

REFERENCES

1. https://pharma.doh.gov.ph/the-national-antibiotic-guidelines/Accessed: January 18, 2023 10:45.
2. https://www.psmid.org/wp-content/uploads/2020/03/CPG-UTI-2013-uncomplicated-part1.pdf Accessed: January 18, 2023 10:52.
3. Alos JI. Epidemiology and etiology of urinary tract infections in the community. Antimicrobial susceptibility of the main pathogens and clinical significance of resistance. Enferm Infecc Microbiol Clin 2005;23(Suppl. 4):3e8.
4. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 2000;10:509e15.
5. Griebling TL. Urologic diseases in America project: trends in resource use for urinary tract infections in women. J Urol 2005;173:1281e7.
6. Valiquette L. Urinary tract infections in women. Can J Urol 2001;8(Suppl. 1):6e12.
7. Little P, Moore MV, Turner S, Rumsby K, Warner G, Lowes JA, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ. 2010;340:c199. https://doi.org/10.1136/bmj.c199.
8. Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. BMJ. 2010;340:b5633. https://doi.org/10.1136/bmj.b5633.
9. Christiaens TCM, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract. 2002;52:729–34.
10. Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?–results of a randomized controlled pilot trial. BMC Med. 2010;8:30. https://doi.org/10.1186/1741-7015-8-30.
11. Knottnerus BJ, Geerlings SE, van Charante EP, ter Riet G. Women with symptoms of uncomplicated urinary tract infection are often willing to delay antibiotic treatment: a prospective cohort study. BMC Fam Pract. 2013;14:71. https://doi.org/10.1186/1471-2296-14-71.
12. Ong DSY, Kuyvenhoven MM, van Dijk L, Verheij TJM. Antibiotics for respiratory, ear and urinary tract disorders and consistency among GPs. J Antimicrob Chemother. 2008;62:587–92. https://doi.org/10.1093/jac/dkn230.
13. Rafal'skiy VV and Khodnevich LV. Acute cystitis: approaches to antimicrobial therapy. Consilium Medicum 2010; 12: 48–53.
14. Kulchavenya EV and Shenchenko SYu. Analysis of results of empiric therapy for out-patients with urogenital infections in a region with high incidence of tuberculosis. Med Educ Siberia (Electronic journal) 2015; 2, http://ngmu.ru/cozo/mos/article/text_full.php?id=1699.
15. Hollis A, Ahmed Z. Preserving antibiotics, rationally. N Engl J Med. 2013;369: 2474–6. https://doi.org/10.1056/NEJMp1311479.
16. Fihn SD, Boyko EJ, Normand EH, et al. Association between use of spermicide-coated condoms and Escherichia coli urinary tract infection in young women. Am J Epidemiol 1996; 144: 512–520.
17. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol. 2000;10:509–15.

18. Leydon GM, Turner S, Smith H, Little P. Women's views about management and cause of urinary tract infection: qualitative interview study. BMJ. 2010; 340:c279. https://doi.org/10.1136/bmj.c279.
19. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scand J Prim Health Care 2007;25:49e57.
20. Christiaens TCM, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract 2002;52:729e34.
21. Asbach HW. Single dose oral administration of cefixime 400 mg in the treatment of acute uncomplicated cystitis and gonorrhoea. Drugs 1991;42(Suppl. 4):10e3.
22. Dubi J, Chappuis P, Darioli R. Treatment of urinary infection with a single dose of co-trimoxazole compared with a single dose of amoxicillin and a placebo. Schweiz Med Wochenschr 1982;112:90e2.
23. Brooks D, Garrett G,Hollihead R. Sulphadimidine,co-trimoxazole, and a placebo in the management of symptomatic urinary tract infection in general practice. J R Coll Gen Pract 1972;22:695e703.
24. Gagyor I, Bleidorn J, Kochen M, Schimmelmann G, Wegscheider K, Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomized controlled trial. BMJ 2015;351:h6544. http://dx.doi.org/10.1136/bmj.h6544.
25. Bleidorn J, Gágyor I, Kochen M, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection? - Results of a randomized controlled pilot trial. BMC Med. 2010;8(30):1–https://doi.org/10.1186/1741-7015-8-30.
26. Vik I, Bollestad M, Grude N, Bærheim A, Damsgaard E, Neumark T, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women—a double-blind, randomized non-inferiority trial. PLoS Med. 2018;15(5):e1002569. https://doi.org/10.1371/journal.pmed.1002569.
27. Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa B, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ. 2017;359:j4784. https://doi.org/10.1136/bmj.j4784.
28. IDSA. https://www.idsociety.org/practice-guideline/uncomplicated-cystitis-and-pyelonephritis-uti/. Accessed: January 20, 2023 20:45.
29. https://synapse.koreamed.org/upload/synapsedata/pdfdata/1216uti/uti-12-55.pdf. Accessed: January 20, 2023 21:15.
30. Center for Health Protection. Accessed: https://www.chp.gov.hk/files/pdf/guidance_notes_acute_uncomplicated_cystitis_in_women_full.pdf. Accessed: January 20, 2023 21:33.
31. Center for Disease Control. https://www.cdc.gov/antibiotic-use/clinicians/adult-treatment-rec.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fantibiotic-use%2Fcommunity%2Ffor-hcp%2Foutpatient-hcp%2Fadult-treatment-rec.html. Accessed: January 20, 2023 21:05.
32. Department of Health-Research Institute for Tropical Medicine. Bacteriology and Antibiogram of Urinary Tract Infection in the Philippines from 2017-2021. Antimicrobial Resistance and Surveillance. February 6, 2023.
33. https://clinicaltrials.gov/ct2/show/NCT01849926?cond=Acute+uncomplicated+cystitis&draw=2&rank=5. Accessed: January 20, 2023 22:11.
34. Seitz M, Stief C and Waidelich R. Local epidemiology and resistance profiles in acute uncomplicated cystitis (AUC) in women: a prospective cohort study in an urban urological ambulatory setting. BMC Infect Dis 2017; 17: 685.
35. Cunha BA, Cunha CB, Lam B, et al. Nitrofurantoin safety and effectiveness in treating acute uncomplicated cystitis (AUC) in hospitalized adults with renal insufficiency: antibiotic stewardship implications. Eur J Clin Microbiol Infect Dis 2017; 36: 1213–1216.
36. Grigoryan L, Zoorob R, Wang H, et al. Less workup, longer treatment, but no clinical benefit observed in women with diabetes and acute cystitis. Diabetes Res Clin Pract 2017; 129: 197–202.
37. Antimicrobial Resistance Surveillance Program Annual Report - 2021. Manila: Antimicrobial Resistance Surveillance Program; 2022.Source: Antimicrobial Resistance Surveillance Program Annual Report - 2021. Manila: Antimicrobial Resistance Surveillance Program; 2022.
38. Kim Do Kyung et.al. Reappraisal of the treatment duration of antibiotic regimens for acute uncomplicated cystitis in adult women: a systematic review and network meta-analysis of 61 randomised clinical trial. Lancet Infec Dis. 2020; DOI:https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30121-3/fulltext

39. https://www.watsons.com.ph/nitrofurantoin-macrocrystals-100mg-1-capsule-prescription-required/p/BP_10000465. Accessed: January 20, 2023 19:45.
40. https://www.watsons.com.ph/fosfomycin-trometamol-3g-granules-for-oral-suspension-1-sachet-prescription-required/p/BP_10096348. Accessed: January 20, 2023 20:12.
41. https://dpri.doh.gov.ph/home/drug_index/791. Accessed: January 20, 2023 20:15.
42. https://www.watsons.com.ph/cefuroxime-500mg-1-tablet-prescription-required/p/BP_10101078. Accessed: January 20, 2023 20:18.
43. https://dpri.doh.gov.ph/home/drug_index/354. Accessed: January 20, 2023 20:20.
44. https://www.watsons.com.ph/cefixime-200mg-1-capsule-prescription-required/p/BP_10098324. Accessed: January 20, 2023 20:21.
45. https://dpri.doh.gov.ph/home/drug_index/333. Accessed: January 20, 2023 20:25.
46. https://www.watsons.com.ph/co-amoxiclav-625mg-1-tablet-prescription-required/p/BP_10095163. Accessed: January 20, 2023 20:28.
47. https://dpri.doh.gov.ph/home/drug_index/447. Accessed: January 20, 2023 20:30.
48. https://www.mims.com/philippines/drug/info/unasyn%20oral?type=full Accessed: March 23, 2023 15:51.
49. https://www.watsons.com.ph/sultamacillin-750mg-1-tablet-prescription-required/p/BP_10095975 Accessed: March 23, 2023 15:58.
50. https://www.watsons.com.ph/ciprofloxacin-hydrochloride-500mg-1-tablet-prescription-required/p/BP_10001964 Accessed: March 23, 2023 16:00.
51. https://dpri.doh.gov.ph/home/drug_2020_index/207 Accessed: March 23, 2023 16:10.
52. https://www.watsons.com.ph/sulfamethoxazole-trimethoprim-400mg-80mg-ml-suspension-60ml-prescription-required/p/BP_50012135 Accessed: March 23, 2023 16:30.
53. https://www.mims.com/philippines/image/info/globaxol%20forte%20oral%20susp/400%20mg-80%20mg-5%20ml%20x%2060%20ml?id=36b4c59c-9cc6-480c-bdc7-a21100dc74e0 Accessed: March 23, 2023 16:33.
54. https://www.mims.com/philippines/drug/info/zolmed-zolmed%20forte Accessed: March 23, 2023 16:45.
55. https://dpri.doh.gov.ph/home/drug_2020_index/245 Accessed: March 23, 2023 16:46.
56. https://dpri.doh.gov.ph/home/drug_2020_index/247 Accessed: March 23, 2023 16:47.
57. https://dpri.doh.gov.ph/home/drug_2020_index/246 Accessed: March 23, 2023 16:48.
58. https://dpri.doh.gov.ph/home/drug_2020_index/248 Accessed: March 23, 2023 16:49.
59. Task Force on UTI 2013. 2013. Philippine Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013 Update: Part 1. Philippine Practice Guidelines Group in Infectious Diseases Philippine Society for Microbiology and Infectious Diseases. Available from: https://www.psmid.org/wp-content/uploads/2020/03/CPG-UTI-2013-uncomplicated-part1.pdf

Question 5. Among adult patients diagnosed with Acute Uncomplicated Pyelonephritis (AUP), should we recommend antibiotics for treatment?

Recommendations

We **suggest** starting with a course of oral fluoroquinolones among adult patients with acute uncomplicated pyelonephritis. *(**Low certainty of evidence, Weak recommendation**)*

Footnote:

- *Some suggested dose and duration of antibiotics for treatment of adult AUP are as follows:*
  - *Ciprofloxacin 500mg BID for 7-10 days PO.*
  - *Ciprofloxacin extended release 1000mg OD for 7 days PO.*
  - *Levofloxacin 250mg OD for 7-10 days PO.*
  - *Levofloxacin 750mg OD for 5 days PO.*
  - *Ofloxacin 400mg BID for 14 days PO.*
- *Use of fluoroquinolones should be evaluated for clinical response (i.e., afebrile, symptom improvement) after 48 hours of therapy. Patient should be admitted if with no improvement as to avoid delay of management.*
- *Urine culture and sensitivity study should be performed prior to antibiotics so that the healthcare provider can shift treatments if needed.*
- *Moxifloxacin is not recommended due to low antibiotic concentration in the urine.*
- *Review local and institutional antibiogram, if available.*

Consensus Issues

- Despite the potential high resistance rates, the panel considered starting with oral fluoroquinolones because the studies reviewed showed high clinical and microbiological cure rates in treating AUP.
- The panel also expressed some concerns on the accuracy of the resistance rates presented in the Annual Resistance Surveillance Program (ARSP) as samples submitted for investigation are often severe and recurrent cases and may not be reflective of the primary care patient presenting with AUP. Hence, the panel emphasized the importance of using local antibiograms to guide the selection of empiric treatment for AUP.
- However, the panel also emphasized the need to monitor for response and immediately adjust therapy based on urine culture and sensitivity, which should always be performed prior to therapy.

KEY FINDINGS

Five RCTs (n=1003) evaluated the comparative effectiveness of several antibiotics in the management of acute uncomplicated pyelonephritis. All antibiotics included in this review (gatifloxacin, ciprofloxacin, levofloxacin, lomefloxacin, rufloxacin, norfloxacin, loracarbef, cefaclor, and trimethoprim/sulfamethoxazole) achieved clinical cure rates higher than 79%. For microbiological cure rates, only fluoroquinolones achieved cure rates above 92%.

Among those who received fluoroquinolones for AUP treatment, thirty-five patients discontinued their participation from the study trials on fluoroquinolones due to moderate to severe adverse drug events (ADEs) (e.g., gastrointestinal, and central nervous system). For the cephalosporin class of antibiotics, three patients required

discontinuation from the study trial due to nausea, vomiting, or rash. Twenty-one patients who received TMP/SMX (11%, n=21/187) also required discontinuation from the study trial due to severe ADEs (e.g., nausea, vomiting, diarrhea, headache, and dizziness).

In another systematic review consisting of RCTs, the risk of gastrointestinal adverse events during UTI treatment was comparable between fluoroquinolone users and TMP-SMX users (n= 809). However, gastrointestinal side effects were significantly higher among fluoroquinolone users compared to macrolides (n=4,682) or cefuroxime axetil users (n=2,441). Overall, compared to other antimicrobials, the risk of gastrointestinal (n=10,616) and CNS-related adverse events (n=9,034) were significantly higher among fluoroquinolone users. Acute psychosis was considered a potential adverse effect of antibiotic treatment of UTIs, although the mechanism remained unknown. Fifteen cases were reported across three classes of antibiotics: fluoroquinolones, penicillin, and TMP-SMX.

INTRODUCTION

Acute uncomplicated pyelonephritis (AUP) is defined as pyelonephritis suspected in otherwise healthy women with no clinical or historical evidence of anatomic or functional urologic abnormalities, who present with the classic syndrome of fever (T ≥38°C), chills, flank pain, costovertebral angle tenderness, nausea, and vomiting, with or without signs and symptoms of lower UTI.[1] Laboratory findings supporting an AUP diagnosis include pyuria (≥5 WBC/HPF of centrifuged urine) on urinalysis and bacteriuria with ≥10,000 CFU/mL counts on urine culture. In one review in the United States, an estimated 10-30% of all patients with AUP are hospitalized, with an incidence of 11.7 per 10,000 for women and 2.4 per 10,000 for men. If AUP is inadequately treated, complications may include progression to bacteremia, development of intra-renal or perinephric abscess, and progression to renal scarring or renal insufficiency. One economic analysis showed that the estimated annual societal cost of pyelonephritis reached 2.14 billion dollars.[2] To prevent additional morbidity and minimize the cost of treatment, it is important to update the antibiotic treatment recommendations for acute uncomplicated pyelonephritis based on efficacy, safety, tolerability, and local antibiotic resistance patterns.

REVIEW METHODS

A systematic search on clinical practice guidelines for acute uncomplicated pyelonephritis in adults was done from January 1, 2017, until November 24, 2022, using Medline, Cochrane Library, Google Scholar with a combined MeSh and free text search using the terms pyelonephritis and guidelines. Prospero and Epistemonikos were also explored for published guidelines related to pyelonephritis. Only clinical practice guidelines in English that contained recommendations on treating acute uncomplicated pyelonephritis in adults were included. The evidence bases of the prioritized guideline were updated. All RCTs that used oral antibiotics for the treatment of AUP until February 2023 were included. For the included studies, follow-up was limited to 14 days. Reports on adverse drug events (ADE) were also incorporated in this review.

RESULTS

Seven updated clinical practice guidelines published from 2017 to November 2022 were found. Using the AGREE-II rating, the clinical practice guidelines of the European Association of Urology (EAU) 2022 on acute uncomplicated pyelonephritis in adults were prioritized for review. Although the NICE guidelines garnered a high-quality rating, this was not prioritized because the evidence presented was taken from RCTs using parenteral antibiotics. The systematic review by Cattrall 2018 formed the basis for most of the EAU's recommendations on the choice of oral antibiotics for AUP. The systematic review by Cattrall until February 1, 2023, was updated, but no additional eligible RCTs were found.

Methodological quality assessment of included studies

The 2022 EAU antibiotic guideline recommendations on oral antibiotics were based on an updated high quality systematic review (Cattral 2018). However, all included RCTs had moderate risk of bias due to a lack of description of their randomization and allocation methodology. Most studies did not report intention-to-treat analysis data. In addition, most studies excluded participants with uropathogens identified as having resistance to the study antibiotics. For the studies on safety of oral antibiotics, a number of studies had moderate risk of bias due to unclear randomization and allocation methods, and non-blinding of participants and outcome assessors. (Appendix 6-7)

Choice of oral antibiotics for AUP (Cattrall 2018, Table 5.1-2)

Fluoroquinolones (Cox, Richard, Bach, Hyslop, Talan)

Gatifloxacin, ciprofloxacin, levofloxacin, lomefloxacin, rufloxacin, and norfloxacin were the six oral fluoroquinolones used in the RCTs included in this review. Four RCTs (Cox, Richard, Bach, Talan) used ciprofloxacin for 7-10 days. Ciprofloxacin had a clinical cure rate of 88-96% (n=187, ffup 4-14 days) and a microbiologic cure rate of 66-100% (n=127, ffup 4-14 days). Likewise, levofloxacin and gatifloxacin achieved high clinical cure rates at 92-100% (n=114, ffup 5-9 days) and high microbiological cure rates at 92-94% (n=114, ffup 5-9 days). Lomefloxacin had clinical cure rates at 80% (n=31/39, ffup 5-9 days). Similarly, rufloxacin and norfloxacin achieved clinical cure rates at 82-84% (n=70, ffup 5-14 days) and microbiological cure rate at 70-77% (n=70, ffup 5-14 days).

In terms of safety, 2-8% (range n=2-10) of the enrolled patients experienced headaches or gastrointestinal side effects (e.g., nausea and vomiting). Thirty-five patients (6%, n=35/628) discontinued their participation from the study trials on fluoroquinolones due to moderate to severe ADEs (e.g., gastrointestinal, and central nervous system).

Cephalosporin (Hyslop)

Loracarbef and cefaclor were the two oral cephalosporins included in this review. With a treatment duration of 14 days, loracarbef had 87% (n=59/68, ffup 5-9 days) clinical cure rate, while cefaclor had 92% (n=23/25, ffup 5-9 days). Compared to fluoroquinolones, microbiologic cure rate was lower for both loracarbef at 81% (n=55/68, ffup 5-9 days), and cefaclor 77% (n=33/43, ffup 5-9 days).

Looking at the safety profile of cephalosporins, nausea was the most reported mild ADE at 3-11% (n=4-5). Three patients required discontinuation from the study trial due to nausea, vomiting, or rash.

Trimethoprim/sulfamethoxazole (TMP/SMX) (Talan)

Treatment with trimethoprim/sulfamethoxazole antibiotic for 14 days achieved a clinical cure rate of 85% (n=66/78, ffup 4-11 days) and microbiologic cure rate of 85% (n=61/72, ffup 4-11 days). However, 7-10% (n=14-19) of those taking trimethoprim/sulfamethoxazole experienced either mild headache or nausea. Twenty-one patients (11%, n=21/187) required discontinuation from the study trial due to severe ADEs.

Table 5.1. Summary of clinical cure rate of oral antibiotics used for treatment of AUP (Adapted from SR – Cattrall, 2018).

Clinical Cure Rate	Study	%	n
Gatifloxacin 400 mg once daily 7-10 days[a]	Cox	100%	25/25
Ciprofloxacin 500 mg twice daily 7 days[b]	Talan	96%	72/75
Ciprofloxacin 500 mg twice daily 7-10 days[a]	Cox	95%	19/20
Ciprofloxacin 500 mg twice daily for 10 days[c]	Bach	94%	32/34
Levofloxacin 250 mg once daily 7-10 days[a]	Richard	92%	82/89
Cefaclor 500 mg thrice daily 14 days minimum[a]	Hyslop	92%	23/25
Ciprofloxacin 500 mg twice daily 10 days[a]	Richard	88%	51/58
Loracarbef 400 mg twice daily 14 days minimum[a]	Hyslop	87%	59/68
Rufloxacin 200 mg once daily 14 days[c]	Bach	85%	23/27
TMP-SMX 160/800 mg twice daily 14 days[b]	Talan	85%	66/78
Norfloxacin 400 mg twice daily 14 days minimum[a]	Hyslop	84%	36/43
Lomefloxacin 400 mg once daily 14 days[a]	Richard	79%	31/39
Adapted from Cattrall 2018 a – ffup 5-9 days b – ffup 4-11 days c – ffup 14 days High cure rate (>90%) – Gupta 2011 IDSA Guidelines Highlighted rows showed high clinical cure rates of >90%			

Table 5.2. Summary of microbiological cure rate of oral antibiotics used for treatment of AUP (Adapted from SR – Cattrall, 2018).

Microbiological Cure Rate	Study	%	n
Ciprofloxacin 500 mg twice daily 7 days[b]	Talan	100%	75/75
Levofloxacin 250 mg once daily 7-10 days[a]	Richard	94%	84/89
Gatifloxacin 400 mg once daily 7-10 days[a]	Cox	92%	23/25
Ciprofloxacin 500 mg twice daily 7-10 days[a]	Cox	85%	17/20
TMP-SMX 160/800 mg twice daily 14 days[b]	Talan	85%	61/72
Loracarbef 400 mg twice daily 14 days minimum[a]	Hyslop	81%	55/68
Lomefloxacin 400 mg once daily 14 days[a]	Richard	79%	31/39
Norfloxacin 400 mg twice daily 14 days minimum[a]	Hyslop	77%	33/43
Cefaclor 500 mg thrice daily 14 days minimum[a]	Hyslop	76%	19/25
Rufloxacin 200 mg once daily 14 days[c]	Bach	70%	19/27
Ciprofloxacin 500 mg twice daily for 10 days[c]	Bach	66%	21/32

Adapted from Cattrall 2018
a – ffup 5-9 days
b – ffup 4-11 days
c – ffup 14 days
High cure rate (>90%) – Gupta 2011 IDSA Guidelines
Highlighted rows showed high microbiological cure rates of >90%

Length of antibiotic treatment for AUP (Berti 2018 – 2 RCTs, Appendix 8: Appendix Table 8.5.6-7)

Based on one RCT on oral antibiotics, short course oral ciprofloxacin for 7 days is not inferior to long course treatment of 14 days (RR 1.01, 95% CI 0.95 – 1.07, high certainty of evidence, ffup 10-14 days). No significant difference is noted on long term follow up at 42-63 days post-treatment (RR 1.00, 95% CI 0.92 – 1.09, high certainty of evidence).[8] Also, clinical cure rates and microbiologic cure rates of short course oral TMP-SMX for 14 days is not significantly different when compared to long course treatment of 6 weeks (RR 1.09, 95% CI 0.81 to 1.45, very low certainty of evidence).[9]

In another systematic review (Erba 2021), short-course antibiotic treatment with either oral or parenteral antibiotics showed a significantly higher clinical cure rate compared to long-course treatment (RR 0.70, 95% CI 0.53 – 0.94, I2=0, 10 RCTs). Also, no significant difference was seen in the rates of microbiological failure using either short-course or long-course antibiotic treatment for AUP (RR 1.06, 95% CI 0.75 – 1.49, I2=55%, 10 RCTs).[10]

Route of antibiotic treatment for AUP (Pohl 2007 – 2 RCTs, Appendix 8: Appendix Table 8.5.8-9)

One study compared oral versus parenteral therapy for patients with AUP. This study by Puppo 1989 compared oral norfloxacin and intravenous aztreonam. The number of patients with microbiological cure at the end of therapy was significantly higher in the parenteral group compared to the oral group (RR 1.38, 95% CI 1.02 – 1.84, low certainty of evidence).[11]

Comparing switch strategy and oral therapy strategy, one study by Mombelli (1999) reported no significant difference (RR 1.04, 95% CI 0.97 - 1.12, high certainty of evidence) between ciprofloxacin oral therapy and switch therapy.[12] In this study, switch therapy with parenteral ciprofloxacin was maintained for a minimum of 72 hours or until afebrile for 24 hours prior to shifting to oral ciprofloxacin.

Safety (Tandan 2018, Mostafa 2014, Table 5.3)

Gastrointestinal adverse events (Tandan)

During UTI treatment, the overall risk of gastrointestinal adverse events was significantly higher among fluoroquinolone users compared to other antimicrobials (OR 1.20, 95% CI 1.06 – 1.36, I^2=84%, n=10,616). Subgroup analysis also showed a significantly higher risk in gastrointestinal adverse events for fluoroquinolone users compared to macrolide users (OR 1.39, 95% CI 1.14 -1.70, I^2=71%, moderate certainty of evidence) and cefuroxime axetil users (OR 1.45 (1.14-1.85), I^2=72%, moderate certainty of evidence). No significant increase in gastrointestinal adverse events for fluoroquinolone users compared to TMP-SMX users (OR 1.01, 95% CI 0.65-1.59, I^2=5%, moderate certainty of evidence). In contrast, the risk for gastrointestinal adverse events was significantly lower for fluoroquinolones users when compared to

co-amoxiclav users (OR 0.69, 95% CI 0.52-0.91, I^2=94%, moderate certainty of evidence).[3]

CNS-related adverse events (Tandan)

The overall risk of CNS-related adverse events was significantly higher among fluoroquinolone users compared to other antimicrobial (OR 1.40, 95% CI 1.12-1.75, I^2=0%, n=9,034). Subgroup analysis showed that risk is increased among fluoroquinolones users compared to those taking macrolides (OR 1.49, 95% 1.02-2.17, I^2=0%, moderate certainty of evidence), cefuroxime axetil (OR 1.77, 95% CI 1.01-3.12, I^2=0%, low certainty of evidence), and co-amoxiclav (OR 1.90, 95% CI 1.03-3.51, I^2=0%, low certainty of evidence). No significant increase in CNS-related adverse events for fluoroquinolone users compared to TMP-SMX users (OR 1.03, 95% CI 0.70–1.52, I2=0%, moderate certainty of evidence).[3]

In another systematic review, Mostafa et al (2014) conducted a search for adverse events related to acute psychosis in patients treated for urinary tract infection. Acute psychosis was considered a potential adverse effect of antibiotic treatment of UTIs, although the mechanism remained unknown. Fifteen cases were reported across three classes of antibiotics: fluoroquinolones (n=8), penicillins (n=2), and trimethoprim-sulfamethoxazole (n=5). Most cases occurred within a week of initiation of antibiotics with prompt resolution upon discontinuation. Half of the cases reported in the review did not require treatment with anti-psychotic agents.

Table 5.3. Summary of safety profile of oral antibiotics used for treatment of AUP (Adapted from SR – Cattrall, 2018).

Antibiotic	Study	Most common adverse events	Drop-out rates due to adverse events
Ciprofloxacin	Cox, Bach, Richard, Talan	Headache, mild (5%, n=9/191 - Talan) Nausea, mild (5%, n=10/191 - Talan) Gastrointestinal, moderate (8%, n= 6/80 - Cox)	Any gastrointestinal or central nervous system ADE (6%, n=11/191 - Talan) Gastrointestinal, moderate (6%, n=10/163 – Cox)
Gatifloxacin	Cox	Nausea (na)	Gastrointestinal (7%, n=12/166)
Levofloxacin	Richard	Flatulence, Vaginitis, Diarrhea, mild (2%, n=3/124)	None reported
Lomefloxacin	Richard	Rash or pruritus, moderate (6%, n=3/55)	Rash or pruritus, moderate (2%, n=1/55)
Norfloxacin	Hyslop	Nausea, mild (2%, n=2/83)	None reported
Rufloxacin	Bach	Insomnia, Dizziness, Sweating (8%, n=4/53)	Insomnia (2%, n=1/53)
Cefaclor	Hyslop	Nausea, mild (11%, n=5/43)	Nausea and vomiting (2%, n=1/43) Rash (2%, n=1/43)

Loracarbef	Hyslop	Nausea, mild (3%, n=4/119)	Nausea and vomiting (1%, n=1/119)
Trimethoprim-sulfamethoxazole	Talan	Headache, mild (10%, n=19/187) Nausea, mild (7%, n=14/187)	Any gastrointestinal or central nervous system ADE (11%, n=21/187)
Adapted from RCTs in Cattrall 2018 na – no data provided.			

RECOMMENDATIONS FROM OTHER GROUPS

Based on the 2013 Philippine Clinical Practice Guidelines on UTI (CPG-UTI) and the 2018 Philippine National Antibiotic Guidelines, fluoroquinolones are recommended as the first-line treatment for AUP not requiring hospital admission.[1,4] Aminopenicillins (ampicillin or amoxicillin) and first-generation cephalosporins are not recommended due to the high prevalence of resistance and recurrence of infection.[1] TMP-SMX is also not recommended as first-line empiric treatment but may be used if the organism is found to be susceptible based on urine culture and sensitivity results. The recommended duration of treatment is 7-14 days.[1] Table 5.4 lists the current empiric oral treatment regimen used for the treatment of acute uncomplicated pyelonephritis in the Philippines.

Table 5.4. Empiric Oral Treatment Regimens for Acute Uncomplicated Pyelonephritis (PSMID 2013)[1,4]

Oral Antibiotics		Dose, Frequency, and Duration
Primary	Ciprofloxacin[a]	500 mg BID for 7-10 days
	Ciprofloxacin extended release	1000 mg OD for 7 days
	Levofloxacin[a]	250 mg OD for 7-10 days
		750 mg OD for 5 days
	Ofloxacin	400 mg BID for 14 days
Alternative	Cefixime[a]	400mg OD for 14 days
	Ceftibuten	400mg OD for 14 days
	Cefuroxime[a]	500mg BID for 14 days
	Co-amoxiclav*[a]	625 mg TID for 14 days
*when gram stain shows gram positive organisms a - recommendations from 2018 Philippine National Antibiotic Guidelines		

Table 5.5. Summary of recommendations from group or agencies

Group or Agency	Recommendation
Philippine Clinical Practice	**ORAL** First-line treatment: -Ciprofloxacin 500 mg twice a day for 7-10 days.

<table>
<tr><td>Guidelines on the Diagnosis of Urinary Tract Infection in Adults 2013 Update</td><td>-Ciprofloxacin extended release 1000 mg once a day for 7 days.
-Levofloxacin 250 mg once a day for 7-10 days.
-Levofloxacin 750 mg once a day for 5 days.
-Ofloxacin 400 mg twice a day for 14 days.

Alternative:
-Cefixime 400 mg once a day for 14 days.
-Ceftibuten 400 mg once a day for 14 days.
-Cefuroxime 500 mg twice a day for 14 days.
-Co-amoxiclav (when gram-staining shows gram-positive organisms) 625 mg three times a day for 14 days.

PARENTERAL (given until patient is afebrile)
First-line treatment:
-Ceftriaxone 1-2 g every 24 hours
-Ciprofloxacin 400 mg every 12 hours
-Levofloxacin 250-750 mg every 24 hours
-Ofloxacin 200-400 mg every 12 hours
-Amikacin 15mg/kg body weight every 24 hours
-Gentamicin +/- ampicillin 3-5 mg/kg body weight every 24 hours

Alternative:
-Ampicillin-sulbactam (when gram-staining shows gram-positive organisms) 1.5 g every 6 hours

Reserved for multi-drug resistant organisms.
-Ertapenem 1 g every 24 hours.
-Piperacillin-tazobactam 2.25-4.5 g every 6-8 hours</td></tr>
<tr><td>2022 European Association of Urology Guidelines on Urological Infections</td><td>• Treat patients with uncomplicated pyelonephritis not requiring hospitalization with short-course fluoroquinolones as first-line treatment.
• Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat AUP.

<table><tr><th>Antimicrobial</th><th>Daily dose</th><th>Duration of therapy</th><th>Comments</th></tr><tr><td>Ciprofloxacin</td><td>500-750 mg b.i.d</td><td>7 days</td><td rowspan="2">Fluoroquinolone resistance should be less than 10%.</td></tr><tr><td>Levofloxacin</td><td>750 mg q.d</td><td>5 days</td></tr><tr><td>Trimethoprim sulfamethoxazol</td><td>160/800 mg b.i.d</td><td>14 days</td><td rowspan="3">If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.</td></tr><tr><td>Cefpodoxime</td><td>200 mg b.i.d</td><td>10 days</td></tr><tr><td>Ceftibuten</td><td>400 mg q.d</td><td>10 days</td></tr></table>b.i.d = twice daily; q.d = every day.</td></tr>
<tr><td>2018 French Infectious Diseases Society</td><td>• For AUP, ciprofloxacin or levofloxacin are recommended as first-line treatment, unless fluoroquinolone was administration <6 months. Grade I-A
• When fluoroquinolones have been administered in the previous 6 months, the alternative parenteral 3rd generation cephalosporin is recommended such as cefotaxime or ceftriaxone.
• When fluoroquinolones and 3rd generation cephalosporins are contraindicated, aminoglycosides or aztreonam should be considered.
• Oral 3rd generation cephalosporins are not recommended as first-line treatment.
• The recommended treatment duration is 7 days for fluoroquinolones and injectable beta-lactam antibiotics, and 10 days for the other antibiotics. (Grade II-B)</td></tr>
<tr><td>2018 Korea CPG for the Antibiotic Treatment</td><td>• All patients with acute pyelonephritis should undergo a urinary culture test before empirical antibiotic administration. (strong recommendation, very low quality)</td></tr>
</table>

of Community-Acquired UTI	• The initial empirical antibiotics administered in the early period of treatment should be adjusted according to the antibiotic susceptibility test results of the causative bacteria. (strong recommendation, very low quality) • For early empirical antibiotic administration for patients with acute pyelonephritis who do not require hospitalization, 1–2 g of intravenous ceftriaxone or 1 dose of amikacin should be administered, followed by oral fluoroquinolone until results are obtained from the culture test. (strong recommendation, very low quality) • For early empirical antibiotic administration for patients with acute pyelonephritis who do not require hospitalization, 400 mg of intravenous ciprofloxacin may be administered, followed by oral ciprofloxacin (500 mg, twice daily) until results are obtained from the culture test.(weak recommendation, very low quality) • If the causative bacteria show susceptibility to antibiotics in the culture test, oral antimicrobial agents such as fluoroquinolone, TMP/SMX, and β-lactams may be used. (strong recommendation, high quality) • If the causative bacteria show susceptibility in patients with acute pyelonephritis, oral antibiotics are administered for 7–14 days. o ciprofloxacin (500 mg, twice daily for 7 days or sustained-release ciprofloxacin, 1000 mg, once daily for 7–14 days) (strong recommendation, high quality) o levofloxacin (500 mg, once daily for 7 days, or 750 mg, once daily for 5 days) (strong recommendation, high quality) o TMP/SMX (160/800 mg, twice daily for 14 days) (strong recommendation, high quality) o Oral β-lactams (10–14 days) (strong recommendation, very low quality)
2018 NICE Guidelines	First line oral Antibiotics for Acute Uncomplicated Cystitis • Cefalexin - 500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infections) for 7 to 10 days. • Co-amoxiclav (only if culture results available and susceptible): 500/125 mg three times a day for 7 to 10 days. • Trimethoprim (only if culture results available and susceptible): 200 mg twice a day for 14 days. • Ciprofloxacin (consider safety issues): 500 mg twice a day for 7 days.
2021 American College of Physicians	• In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP–SMZ (14 days) based on antibiotic susceptibility.
2018 German Guidelines	Oral treatment in mild to moderate infections • Ciprofloxacin 500-750mg twice a day for 7-10 days • Levofloxacin 750mg once a day for 5 days • Cefpodoxim-proxetil 200mg twice a day for 10 days • Ceftibuten 400mg once a day for 10 days
2022 Japan Guidelines	Mild and moderate cases of acute uncomplicated pyelonephritis • In mild and moderate cases of AUP, oral therapy for 7-14 days is usually sufficient. • A fluoroquinolone for 7-14 days can be recommended if the resistance of E. coli is <10%. • Treatment duration can be reduced to 5-7 days for high dose fluoroquinolones. • If prevalence of fluoroquinolone resistance exceeds 10%, 1g of ceftriaxone or an aminoglycoside is recommended as an initial one-time intravenous agent. • Oral β-lactam agents are often less effective than other available agents for treatment of pyelonephritis If an oral β-lactam agent is used, an initial intravenous long-acting antimicrobial agent or a consolidated aminoglycoside is recommended.

	• Oral trimethoprim-sulfamethoxazole (160/800 mg [1 double strength tablet] twice-daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible. Oral therapy in mild and moderate cases: • Ciprofloxacin 500mg twice a day or 1000mg once a day for 7-10 days • Levofloxacin 500-750mg once a day for 7-10 days Alternatives • Ceftibuten 400mg once a day for 10 days • Ceftitoren pivoxil 200mg thrice a day for 14 days Only if pathogen is known susceptible (not for initial empiric therapy) • TMP-SMX 160/800mg thrice a day for 14 days • Amoxicillin/Clavulanic acid 875mg-2000mg/125mg twice a day for 14 days

ONGOING STUDIES AND RESEARCH GAPS

No on-going randomized controlled trials were found on the use of oral antibiotics for acute pyelonephritis in adults.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Local resistance pattern of oral antibiotics

Based on a recent systematic review by Cattrall et al in 2018, *E. coli* was the most frequently isolated organism from those with AUP (range 56.4-92.5%).[5] This is consistent with the local 2021 Antimicrobial Resistance Surveillance Program (ARSP) that also showed *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter* sp. as the top three most common organisms isolated from urine cultures (Table 5.6). Local data showed *E. coli* has favorable susceptibility to nitrofurantoin, ampicillin-sulbactam and co-amoxiclav. In contrast, cefazolin, cefuroxime, and ciprofloxacin had high resistance rates 39.7–48.9%. Overall, *E. coli* has the highest resistance to TMP-SMX with resistance rates at 55.2%.

The Philippine CPG-UTI of 2013 noted that the high rates of *E. coli* resistance to ciprofloxacin (50.6%) may not be representative of the true prevalence of the resistance rates in the community since the *E. coli* isolates were submitted from government hospitals and may not be limited to patients with uncomplicated UTI. Compared to the ARSP survey, one prospective cohort study in 2015 on acute uncomplicated urinary tract infection and acute pyelonephritis from patients seen in a private tertiary hospital in Pasig City reported lower fluoroquinolone resistance prevalence at 10%.[6]

Table 5.6. Oral antibiotics E-coli resistance rate in urine isolates of out-patients (ARSP, 2021)

Drugs	% Resistance
Nitrofurantoin (n=373)	5.9%
Ampicillin Sulbactam (n=165)	14.5%
Amoxicillin Clavulanic (n=616)	20.5%

Cefuroxime (n=58)	39.7%
Ciprofloxacin (n=617)	48.9%
Co-trimoxazole (n=616)	55.2%
Source: Antimicrobial Resistance Surveillance Program Annual Report - 2021. Manila: Antimicrobial Resistance Surveillance Program; 2022. ** *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter* sp. are the top three most common organisms isolated from urine cultures	

Cost

No relevant evidence regarding the cost-effectiveness of fluoroquinolones for the treatment of UTIs was identified.

Patient's values and preference, equity, acceptability, and feasibility

Based on one discrete choice experiment study(n=833), women were willing to accept UTI management with a higher chance of complication or longer time to resolution, if it could help avoid antimicrobial resistance. Most women who had one previous UTI had a stronger preference for a treatment that resulted in a faster symptom resolution compared to those who had no previous history of UTI. Younger women compared to older women also preferred faster symptom resolution. Women with low or middle education level also gave less importance to prevention of antimicrobial resistance compared to those with higher educational attainment.[7]

REFERENCES

1. in Adults 2013 Update PPGG-ID Philippine Society for Microbiology and Infectious Diseases. Quezon City: 2013.
2. 2Brown P, Ki M, Foxman B. Acute pyelonephritis among adults: cost of illness and considerations for the economic evaluation of therapy. Pharmacoeconomics 2005;23:1123–42. doi:10.2165/00019053-200523110-00005
3. 3Tandan M, Cormican M, Vellinga A. Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: A systematic review and meta-analysis of randomized controlled trials. Int J Antimicrob Agents 2018;52:529–40. doi:10.1016/J.IJANTIMICAG.2018.04.014
4. Department of Health Philippines. National Antibiotic Guidelines 2018. National Antibiotic Guidelines Committee 2018.
5. Cattrall JWS, Robinson A v., Kirby A. A systematic review of randomised clinical trials for oral antibiotic treatment of acute pyelonephritis. Eur J Clin Microbiol Infect Dis 2018;37:2285–91. doi:10.1007/S10096-018-3371-Y
6. Gangcuangco LM, Alejandria M, Henson KE, et al. Prevalence and risk factors for trimethoprim–sulfamethoxazole-resistant Escherichia coli among women with acute uncomplicated urinary tract infection in a developing country. International Journal of Infectious Diseases 2015;34:55–60. doi:10.1016/J.IJID.2015.02.022
7. Van Der Worp H, Brandenbarg D, Boek PA, et al. Identifying women's preferences for treatment of urinary tract infection: a discrete choice experiment. doi:10.1136/bmjopen-2021-049916
8. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet 2012;380:484–90. doi:10.1016/S0140-6736(12)60608-4
9. Stamm WE, McKevitt M, Counts GW. Acute renal infection in women: Treatment with trimethoprim-sulfamethoxazole or ampicillin for two or six weeks. A randomized trial. Ann Intern Med 1987;106:341–5. doi:10.7326/0003-4819-106-3-341
10. Erba L, Furlan L, Monti A, et al. Short vs long-course antibiotic therapy in pyelonephritis: a comparison of systematic reviews and guidelines for the SIMI choosing wisely campaign. Intern Emerg Med 2021;16:313–23. doi:10.1007/S11739-020-02401-4

11. Puppo P, Germinale F, de Rose AF. [Aztreonam vs norfloxacin: a comparative study of the treatment of urinary tract infections in ambulatory and hospitalized patients]. Clin Ter 1989;129:113–21.https://europepmc.org/article/med/2525996 (accessed 18 Feb 2023).
12. Mombelli G, Pezzoli R, Pinoja-Lutz G, et al. Oral vs Intravenous Ciprofloxacin in the Initial Empirical Management of Severe Pyelonephritis or Complicated Urinary Tract Infections: A Prospective Randomized Clinical Trial. Arch Intern Med 1999;159:53–8. doi:10.1001/archinte.159.1.53
13. Task Force on UTI 2013. 2013. Philippine Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2013 Update: Part 1. Philippine Practice Guidelines Group in Infectious Diseases Philippine Society for Microbiology and Infectious Diseases. Available from: https://www.psmid.org/wp-content/uploads/2020/03/CPG-UTI-2013-uncomplicated-part1.pdf

Question 6. Among pediatric patients diagnosed with Acute Uncomplicated Cystitis (AUC), should we recommend antibiotics for treatment?

Recommendations

We **recommend** the use of oral antibiotics for the treatment of acute urinary cystitis in children (***Best Practice Statement***).

Consensus issues

- The panel decided on a best practice statement for recommending antibiotics in children with AUC, in the absence of trial evidence showing clear benefit, in consideration of the overall perceived balance of benefit and harm, acceptability, resource use and equity in favor of antibiotic treatment.
- Despite the very low certainty of evidence for specific antibiotic treatment, the panel decided to recommend the use oral antibiotics for AUC in children since there is a need to treat to prevent further complications.
- Since cystitis usually has lower urinary tract manifestation, the panel was concerned that patients younger than 2 years old may have difficulty verbalizing their symptoms and will make it hard to determine if it is AUC or not.

Recommendations

We **suggest** either short course (3-7 days) or conventional 10-day course of oral antibiotics for the treatment of acute uncomplicated cystitis in children *(**Very low certainty of evidence, Weak recommendation**)*

Footnote:

- *Shift to IV medications if oral medication is not tolerated, and in children who are very sick looking, have persistent vomiting and in those who are less than 8 weeks old.*

Consensus Issues

- The panel recognized the paucity of available data and emphasized the need to use good clinical judgment on the treatment duration, in consideration of antimicrobial resistance rates.

Recommendations

We **suggest** the following antibiotics in the management of acute uncomplicated cystitis in children:

- Nitrofurantoin
- Ampicillin-Sulbactam
- Co-amoxiclav
- Cefuroxime

*(**Very low certainty of evidence, Weak recommendation**)*

Footnote:

- *Some suggested dose and duration of antibiotics for treatment of pediatric AUC are as follows:*
  - *Nitrofurantoin 5-7 mg/kg/day divided into 3 to 4 divided doses PO.*
  - *Co-amoxiclav 30-50 mg/kg/day in 2 divided doses PO.*

- *Cefuroxime 20-30mg/kg/day in 2 divided doses PO; same with adult dosing if ≥40kg.*
- *Ampicillin-sulbactam: Ampicillin 100mg/kg/day divided in 4 doses IV if oral medications are not tolerated.*

- *Review local and institutional antibiograms, if available.*
- *Antibiotic treatment should be switched appropriately as soon as culture study results are available.*

KEY FINDINGS

Evidence is based on the 2012 Cochrane systematic review and meta-analysis on antibiotics use for lower urinary tract infection in children. Pooled analysis showed significant risk for persistent bacteriuria when giving single dose of antibiotics compared to 10-day conventional treatment, but no difference was found in terms of persistence of symptoms and recurrence of infection. No significant difference was found in terms of persistence of symptoms, recurrence, and re-infection short term (3-7 days) antibiotics was compared to single-dose and long course (10-14 days) antibiotics. In terms of choice of antibiotics, no difference was found between single dose intramuscular fosfomycin vs netilmicin and 10-day oral cefadroxil vs ampicillin in terms of persistence of bacteriuria, persistence of symptoms, and recurrence of UTI. Certainty of evidence was downgraded to very low due to moderate risk of bias, inconsistency, and imprecision.

INTRODUCTION

Acute uncomplicated cystitis or lower urinary tract infection is defined as bacteriuria without fever or loin pain, but with localizing signs such as dysuria, frequency, urgency, and lower abdominal discomfort.[1] These localizing symptoms are observed more in the older age group, but children younger than 2 years old may present with non-specific illness such as fever, irritability, lethargy, vomiting, and/or diarrhea.[2] Laboratory findings supporting UTI in children include pyuria (≥5 WBC/hpf in centrifuged urine or >10 WBC/mm3 in uncentrifuged urine) and bacteriuria of ≥50,000 CFUs/ml for catheterized samples, $\geq 10^5$ CFUs/ml for clean-catch samples, or any growth in suprapubic aspirate.[2] Locally, the incidence rate of UTI in the pediatric age group is 30 per 1000 persons, 54% of which were female, and majority were between 7 to 12 years of age.[3] Inadequately treated cystitis may lead to further complications, including pyelonephritis, urosepsis, abscesses, renal scarring, and chronic renal disease. Local recommendations by the Philippine Pediatric Society for the treatment of UTI in children were published in 2004 and updates on recommendations in antibiotic therapy, including route, duration, efficacy, and safety of antibiotics specific to acute urinary cystitis is needed.

REVIEW METHODS

A systematic search was done from the last published clinical practice guideline in 2004 until March 31, 2023, using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms pediatric, children, cystitis, lower urinary tract infection, antibiotics, and anti-infective agents. Ongoing studies were explored through the NIH clinicaltrials.gov and other trial registries. Preprints were also searched using medrxiv. Only randomized controlled trials and systematic reviews and meta-analyses in English on the antibiotic treatment of acute urinary cystitis or lower urinary tract infection in children were included. One systematic review and meta-

analysis was found on the use of antibiotics for lower urinary tract infection or acute urinary cystitis.[4] This review was appraised as high-quality using AMSTAR 2. A systematic search was done after their last search which yielded no additional studies.

RESULTS

Fourteen randomized controlled trials and quasi-RCTs of children aged 0 to 18 years in primary and community healthcare setting with bacteriologically proven symptomatic lower UTI (n=1,116) were included in the review. There were no studies found comparing antibiotics with placebo or other pharmacologic intervention. Studies found compared the effectiveness of different antibiotic therapies or the duration of therapy (single dose, short course 3-7 days, and conventional 10-day course). The outcomes were: persistent symptoms, persistent bacteriuria, recurrence following treatment, and re-infection following treatment.[5-18] Six studies used penicillin (amoxicillin, ampicillin, pivmecillinam), four studies used cephalosporins (cephalexin, ceftriaxone, cefadroxil), three studies included aminoglycosides (gentamicin, amikacin, netilmicin), three studies included sulfonamides +/- trimethoprim, one study included trimethoprim only, and one study included Fosfomycin.

Specific antibiotics for pediatric AUC

Only 2 studies compared different antibiotics given at the same duration.[13,15] Cefadroxil versus ampicillin given for 10 days, and showed no difference in terms of persistent bacteriuria (RR 0.33, 95% CI 0.01 to 7.62) and persistence of symptoms (RR 0.33, 95% CI 0.01 to 7.62).[13] Meanwhile, there was no difference between single-dose fosfomycin versus netilmicin in terms of persistent bacteriuria (RR 3.15, 95% CI 0.68 to 14.64) and risk of recurrence (RR 0.63, 95% CI 0.26 to 1.56).[13]

Duration of antibiotics for pediatric AUC

Single-dose versus 10-day treatment

Six RCTs compared single-dose versus conventional 10-day treatment duration. [5,7,11,16-18] For the single dose, four studies made use of oral antibiotics (amoxicillin), while two studies gave the antibiotics intramuscularly. Pooled analysis showed significant risk for persistent bacteriuria (RR 2.01, 95% CI 1.06 to 3.80, I^2 = 0%) for patients given single-dose antibiotics compared to those given the conventional 10-day course. Evidence was inconclusive in terms of persistent symptoms (RR 0.29, 95% CI 0.03 to 2.50, I^2 = 0%) and risk of recurrence (RR 1.38, 95% CI 0.55 to 3.50, I^2 = 0%).

Single-dose versus short course (3-7 days) treatment

Two RCTs compared single-dose versus short course treatment of 3-7 days.[8,12] Grimwood et al. compared single-dose intramuscular gentamycin vs any conventional antibiotic given for 7 days, [8] while Lidefelt et al. compared trimethoprim given as single dose versus 5 days.[12] Pooled analysis showed inconclusive results in terms of persistent bacteriuria (RR 1.03, 95% CI 0.65 to 2.62, I^2 = 30%) and recurrence (RR 1.50, 95% CI 0.43 to 5.26, I^2 = 29%). Grimwood et al. showed inconclusive results in terms of re-infection after treatment (RR 0.16, 95% CI 0.02 to 1.26).

Short course (3-7 days) versus long course (10 days) treatment

Four RCTs compared short (3-7 days) versus long (10-14 days) duration of treatment.[6,9,10,14] Mitnik et al. compared 3-day, 5-day, and 10-day course,[14] while the other studies compared 3-day versus 10-day duration. Various antibiotics were used in the included studies. Pooled analysis showed inconclusive results in terms of persistent bacteruria (RR 1.09, 95% CI 0.67 to 1.76, I2 = 0%), recurrence (RR 1.25, 95% CI 0.74 to 2.13, I^2 = 0%), and re-infection after treatment (RR 0.88, 95% CI 0.44 to 1.74, I^2 = 0%).

Adverse events duration

Adverse events were reported in 10 studies, but only 4 studies can be pooled for each comparison. Results were inconclusive for single vs 10-day treatment duration with amoxicillin (RR 1.25, 95% CI 0.74 to 2.13). Candida vaginitis was observed in 3 patients who were given 10 days of amoxicillin vs those given as single dose. Meanwhile, results were also inconclusive for patients given short vs long course of antibiotics (RR 11.29, 95% CI 0.65 to 197.19). Patients given short course of pivmecillinam reported urticarial rash (n=2), vomiting (n=2), diarrhea (n=1), and irritability and fatigue (n=1).

CERTAINTY OF EVIDENCE

Certainty of evidence was downgraded to very low due to inconsistency (moderate heterogeneity), imprecision (wide confidence intervals), and moderate risk of bias due to lack of reporting of randomization methodology, concealment, and blinding. There were also inadequate follow-ups in 3 studies.

RECOMMENDATIONS FROM OTHER GROUPS

These were the recommendations from other groups. Recommendations from the Philippine Pediatric Society, American Academy of Pediatrics, and Italian Society of Pediatric Nephrology includes all urinary tract infections and were not specific for acute urinary cystitis.

Table 6.1. Summary of recommendations from groups or agency.

Group or Agency	Recommendations
Philippine Pediatric Society 2004 [2]	No recommendations on duration and route of antibiotics specific for acute cystitis Suggested oral antimicrobials for the treatment of UTI: • Amoxicillin 20-40mg/kg/day in 3 doses • TMP+SMX 6-12mg/30-60mg/kg/day in 2 doses • Sulfisoxazole 120-150mg/kg/day in 4 doses • Cefixime 8mg/kg/day in 2 doses • Cephalexin 50-100mg/kg/day in 4 doses • Cefpodoxime 10mg/kg/day in 2 doses • Cefprozil 30mg/kg/day in 2 doses • Loacarbef 150-300mg/kg/day in 2 doses

American Academy of Pediatrics 2011 [19]	**Duration of antibiotics** The clinician should choose 7 to 14 days as the duration of antimicrobial therapy (evidence quality: B; recommendation). **Route of antibiotics** The clinician should base the choice of route of administration on practical considerations. Initiating treatment orally or parenterally is equally efficacious. **Choice of antibiotics** The clinician should base the choice of agent on local antimicrobial sensitivity patterns (if available) and should adjust the choice according to sensitivity testing of the isolated uropathogen (evidence quality: A; strong recommendation).
NICE Guidelines 2022 [20]	**Route and duration of antibiotics** For children aged >3 months with lower UTI, oral antibiotics for 3 days is advised. Take account of the following: • Previous urine culture and susceptibility results • Previous antibiotic use, which may have led to resistant bacteria **Choice of antibiotics** Trimethoprim (if there Is low risk of resistance) • 3 months to 5 months, 4 mg/kg (maximum 200 mg per dose) or 25 mg twice a day for 3 days • 6 months to 5 years, 4 mg/kg (maximum 200 mg per dose) or 50 mg twice a day for 3 days • 6 years to 11 years, 4 mg/kg (maximum 200 mg per dose) or 100 mg twice a day for 3 days • 12 years to 15 years, 200 mg twice a day for 3 days **Nitrofurantoin (if eGFR is 45ml/min or more)** • 3 months to 11 years, 750 micrograms/kg four times a day for 3 days • 12 years to 15 years, 50 mg four times a day or 100 mg modified-release twice a day for 3 days
KHA-CARI guideline Australia 2014 [1]	**Route and duration of antibiotics** Short duration oral therapy (2-4 days) for treating lower UTI, as it is as effective as standard duration therapy (7-14 days)
Italian Society of Pediatric Nephrology 2019 [21]	**Route of antibiotics** If the UTI is not complicated, that is when the febrile child is in good clinical condition and able to retain oral fluids and medications and compliance is expected, treatment should be administered via the oral route (Grade A) **Choice of antibiotics** First line: Amoxicillin-clavulanic acid (50-90mg/kg/day of amoxicillin) in 3 doses Base choice on local antimicrobial sensitivity patterns (if available) and adjust it according to sensitivity testing of the isolated uropathogen

ONGOING STUDIES AND RESEARCH GAPS

No on-going randomized controlled trials were found on the use of antibiotics for acute urinary cystitis in children.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No evidence regarding the cost-effectiveness of antibiotics for the treatment of acute urinary cystitis were found.

Patient's values and preference, equity, acceptability, and feasibility

A multicenter prospective observational study done on acceptability of oral antibiotics in children from various countries in Europe and Asia and the Pacific [22] showed differences in acceptability based on age groups. Patient reaction was negative for 23% of grade-schoolers, 35% of toddlers and preschoolers, and 43% of infants, although required dosage was fully taken by 96% of grade-schoolers, 81% of toddlers and 77% of infants and newborns. Solid oral dosage forms were accepted more by grade-schoolers compared to liquid forms, while no difference was found between reconstituted oral liquids versus ready-to-use liquid forms among toddlers and preschoolers.

REFERENCES

1. McTaggart S, Danchin M, Ditchfield M, Hewitt I, Kausman J, Kennedy S, et al. (Kidney Health Australia -– Caring for Australasians with Renal Impairment). KHA-CARI guideline: Diagnosis and treatment of urinary tract infection in children. Nephrology (Carlton). 2015; 20(2): 55-60.
2. Philippine Pediatric Society. Clinical practice guidelines in the approach and treatment of urinary tract infection in children in the Philippines. 2004. PPS
3. Bay A, Anacleto F. Clinical and laboratory profile of urinary tract infection among children at the outpatient clinic of a tertiary hospital. Pediatric Infectious Disease Society of the Philippines Journal. 2010; 11(1): 10-16
4. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. Cochrane Database Syst Rev. 2012; 8:CD006857
5. Avner ED, Ingelfinger JR, Herrin JT, Link DA, Marcus E, Tolkoff-Rubin NE, et al.Single-dose amoxicillin therapy of uncomplicated pediatric urinary tract infections. Journal of Pediatrics 1983;102(4):623–7.
6. Copenhagen Study Group. Short-term treatment of acute urinary tract infection in girls. Copenhagen Study Group of Urinary Tract Infections in Children. Scandinavian Journal of Infectious Diseases 1991;23(2):213–20.
7. Fine JS, Jacobson MS. Single-dose versus conventional therapy of urinary tract infections in female adolescents. Pediatrics 1985;75(5):916–20.
8. Grimwood K, Abbott GD, Fergusson DM. Single dose gentamicin treatment of urinary infections in children. New Zealand Medical Journal 1988;101(852):539–41.
9. Helin I. Three-day therapy with cephalexin for lower urinary tract infections in children. Scandinavian Journal of Infectious Diseases 1984;16(3):305–7.
10. Khan AJ, Kumar K, Evans HE. Three-day antimicrobial therapy of urinary tract infection. Journal of Pediatrics 1981; 99(6):992–4.
11. Komoroski EM, Lensing SY, Portilla MG, Krebel MS, Krebel SR, Kearns GL. Single-dose intramuscular ceftriaxone for the treatment of uncomplicated cystitis in children and adolescents. Current Therapeutic Research -– Clinical & Experimental 1999;60(11):580–54.
12. Lidefelt KJ, Bollgren I, Wiman A. Single dose treatment of cystitis in children. Acta Paediatrica Scandinavica 1991;80 (6-7):648–53.
13. Malaka-Zafiriu K, Papadopoulos F, Avgoustidou- Savopoulou P, Papachristos F. Comparison of cefadroxil and ampicillin in the treatment of urinary tract infections in children. Clinical Therapeutics 1984;6(2):178–84.
14. Mitnik M, Gasc O, Gonzalez A. Short-course treatment of urinary tract infections in children [Tratamiento abreviado de la infeccion del tracto urinario en ninos]. Pediatria 1985; 28(3-4):94–6.
15. Principi N, Corda R, Bassetti D, Varese LA, Peratoner L. Fosfomycin trometamol versus netilmicin in children's lower urinary tract infections. Chemotherapy 1990;36 Suppl 1: 41–5.

16. Shapiro ED, Wald ER. Single-dose amoxicillin treatment of urinary tract infections. Journal of Pediatrics 1981;99(6): 989–92.
17. Stahl GE, Topf P, Fleisher GR, Norman ME, Rosenblum HW, Gruskin AB. Single-dose treatment of uncomplicated urinary tract infections in children. Annals of Emergency Medicine 1984;13(9 Pt 1):705–8.
18. Wallen L, Zeller WP, Goessler M, Connor E, Yogev R. Single-dose amikacin treatment of first childhood E. coli lower urinary tract infections. Journal of Pediatrics 1983; 103(2):316–9.
19. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management; Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011 Sep;128(3):595-610
20. National Institute for Health and Care Excellence. NICE Guidelines: Urinary tract infection in under 16s: diagnosis and management. 2022. Accessed from: www.nice.org.uk/guidance/ng224
21. Ammenti A, Alberici I, Brugnara M, Chimenz R, Guarino S, La Manna A, et al. Italian Society of Pediatric Nephrology. Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatr. 2020;109(2):236-247.
22. Vallet T, Bensouda Y, Saito J, Mathiesen L, Pokharkar V, Klingmann V, et al. Exploring Acceptability Drivers of Oral Antibiotics in Children: Findings from an International Observational Study. Pharmaceutics. 2021;13(10):1721

Question 7. Among pediatric patients diagnosed with Acute Uncomplicated Pyelonephritis (AUP), should we recommend oral antibiotics for treatment?

Recommendations

We **suggest** the use of either short course (3-4 days) intravenous antibiotics followed by oral antibiotics OR oral antibiotics to complete 7-10 days treatment duration for children with acute pyelonephritis. *(**Low certainty of evidence, Weak recommendation**)*

Recommendations

We **suggest** the use of the following antibiotics as empiric treatment regimen for children with acute pyelonephritis:

- Ampicillin-Sulbactam
- Cefuroxime
- Ceftriaxone
- Cefixime
- Co-amoxiclav
- Amikacin (for those with beta-lactam allergies)

*(**Low certainty of evidence, Weak recommendation**)*

Footnote:

- *Some dosage and duration of antibiotic treatment for pediatric AUP are as follows:*
  - *Nitrofurantoin 5-7 mg/kg/day divided into 3 to 4 divided doses PO.*
  - *Ampicillin-sulbactam: Ampicillin 100mg/kg/dose in 4 divided doses IV.*
  - *Co-amoxiclav 30-50 mg/kg/day in 2 divided doses PO.*
  - *Cefuroxime 20-30 mg/kg/day in 2 divided doses PO; same with adult dosing if ≥40kg.*
  - *Ceftriaxone 50-75 mg/kg/day in 2 divided doses IV.*
  - *Cefixime suspension 8 mg/kg/day in 2 divided doses PO.*
  - *Amikacin 15-22.5 mg/kg/day divided in 2 to 3 doses IV.*
- *Review local and institutional antibiograms, if available.*
- *Antibiotic treatment should be switched appropriately as soon as culture study results are available.*

KEY FINDINGS

This evidence was based on twenty-five randomized controlled trials of children with acute pyelonephritis (n=4,211) Pooled analysis showed that third generation cephalosporins had significant benefit over other antibiotics in terms of risk for persistent symptoms after end of treatment. No significant difference was found between cefepime and ceftazidime in terms of persistence or recurrence of initial pathogen and infection with a new pathogen at 4-6 weeks post-treatment (RR 1.19, 95% Ci 0.45 to 3.18). No significant difference was also found between ceftriaxone and cefotaxime in terms of persistent bacteriuria and UTI recurrence. Results were inconclusive when comparing aminoglycoside dosing regimens in terms of time to fever resolution, persistent bacteriuria, persistence of symptoms, reinfection, and kidney parenchymal damage. Results were inconclusive in terms of persistent bacteriuria, recurrent bacteriuria and symptoms, relapse/reinfection, and persistent kidney damage at 3-6 months for single intravenous dose versus oral 7 to 10-day

course, short versus long intravenous course, and 2-week versus 3-week antibiotic course. Likewise, results were inconclusive in terms of time to fever resolution, persistent and recurrent UTI, and persistent kidney damage at 3-6 months when only oral antibiotics are given versus intravenous antibiotics followed by oral step-down, and single dose intramuscular antibiotics followed by oral step-down. Certainty of evidence was downgraded to very low to low due to inconsistency, imprecision, and moderate risk of bias.

INTRODUCTION

In acute pyelonephritis or upper UTI, the infection occurs within the kidney parenchyma and is clinically characterized by systemic symptoms such as fever (>38C), body malaise, vomiting, abdominal pain, and loin tenderness.[1] However, children younger than 2 years old may also present with other non-specific illness such as irritability, lethargy, and/or diarrhea.[2] Laboratory findings supporting UTI in children include pyuria (≥5 WBC/hpf in centrifuged urine or >10 WBC/mm3 in uncentrifuged urine) and bacteriuria of ≥50,000 CFUs/ml for catheterized samples, ≥10^5CFUs/ml for clean-catch samples, or any growth in suprapubic aspirate.[2] Locally, the incidence rate of UTI in the pediatric age group is 30 per 1000 persons.[3] Inadequate treatment of pyelonephritis may lead to short-term complications such as urosepsis and acute kidney injury, as well as long-term sequelae such as vesicoureteral reflux, renal scarring on DMSA scans, recurrent infections, and end-stage renal disease.[4,5] Updates on local recommendations in antibiotic therapy, including route, duration, efficacy, and safety of antibiotics specific to acute pyelonephritis is needed.

REVIEW METHODS

A systematic search was done from the last published clinical practice guideline in 2004 until June 23, 2023, using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms pediatric, children, pyelonephritis, uncomplicated pyelonephritis, urinary tract infection, antibiotics, and anti-infective agents. Ongoing studies were explored through the NIH *clinicaltrials.gov* and other trial registries. Preprints were also searched using medrxiv. Only randomized controlled trials and systematic reviews and meta-analyses in English on the antibiotic treatment of acute uncomplicated pyelonephritis or in children were included. One Cochrane meta-analysis was found on the use of antibiotics for acute pyelonephritis in children.[6] This review was appraised as high-quality using AMSTAR 2.

A systematic search was done after the last search of this meta-analysis (April 10, 2014) until July 2, 2023, which yielded two additional randomized controlled trials on cephalosporin and beta lactamase inhibitor combinations against acute pyelonephritis. Bradley et al. evaluated the safety and efficacy of ceftazidime-avibactam in infants and children with complicated UTI including acute pyelonephritis compared to cefepime.[7] Roilides et al. ceftolozane-tazobactam versus meropenem for complicated UTI including pyelonephritis.[8] The cure rates of the individual antibiotic were extracted from each of the RCTs and presented as pooled estimate using Stata 15.1.

RESULTS

Twenty-five randomized controlled trials of children aged 0 to 18 years old with bacteriologically/culture-proven symptomatic pyelonephritis (n=4,211) were included

in the review.[7-31] Patients received either inpatient treatment (7 studies), outpatient treatment (2 studies), or both (16 studies). Sixteen studies used cephalosporins, 8 studies used aminoglycosides, 6 studies used trimethoprim-sulfamethoxazole (TMP-SMX), 5 studies used amoxicillin or amoxicillin-clavulanic acid, 2 studies used combination cephalosporin-beta lactamase inhibitors, and 1 study used carbapenem. There were no studies found comparing antibiotics with placebo. RCTs compared the effectiveness of different antibiotic therapies, route of administration (oral only or IV followed by oral), and the duration of therapy (single IV dose vs 7-10 days oral course, short 3-4 days vs long IV course 7-14 days, or 2-week vs 3-week course). The outcomes were: time to fever resolution, persistent UTI/bacteriuria, persistent symptoms, reinfection, recurrent UTI at 1 or 6 months, and kidney damage at 3 or 6 months.[9-31] Two studies looked into outcomes of good clinical response at 72 hours, at test of cure, and on late follow-up.[7,8] Nine studies evaluated adverse events.

EFFICACY OUTCOMES

Duration of antibiotics for pediatric pyelonephritis

There were inconclusive results in terms of persistent bacteriuria, recurrent bacteriuria and symptoms, relapse/reinfection, and persistent kidney damage at 3-6 months for single intravenous dose versus oral 7 to 10-day course, short versus long intravenous course, and 2-week versus 3-week antibiotic course.

Single-dose intravenous versus 7-10 days oral antibiotic treatment

Two RCTs compared single IV antibiotic dose versus 7-10 days oral antibiotic treatment duration.[19,20] For the single dose, 1 study made use of IV gentamicin,[19] while the other study made use of IV cefotaxime.[20] These were compared to various oral antibiotics. Pooled analysis showed inconclusive results in terms of persistent bacteriuria at 48 hours (RR 1.73, 95% CI 0.18 to 16.30, I^2 = 0%) and relapse or reinfection at 6 weeks (RR 0.24, 95% CI 0.03 to 1.97).

Short (3-4 days) versus long (7-10 days) intravenous course

Six RCTs compared intravenous course (3-4 days) followed by oral step-down to complete 7-10 days course of antibiotics versus long 7-10 days intravenous antibiotics course.[15,21-25] Two studies used cephalosporins,[21,22] 2 RCTs used cephalosporin together with aminoglycoside,[23,24] 1 study used IV temocillin followed by oral amoxicillin,[25] while one study compared short-course IV cephalosporin followed by oral cephalosporin versus long course IV ampicillin with aminoglycoside.[15] Pooled analysis showed inconclusive results in terms of persistent bacteriuria after treatment (RR 0.78, 95% CI 0.24 to 2.55, I^2 = 0%), recurrent UTI at 6 months (RR 0.97, 95% CI 0.58 to 1.62, I^2 = 0%), and persistent kidney damage at 3-6 months (RR 1.01, 95% CI 0.80 to 1.29, I^2 = 0%). Subgroup analysis of patients with renal parenchymal damage on initial DMSA scan showed no difference between short versus long intravenous course in terms of persistent kidney damage at 3-6 months (RR 1.10, 95% CI 0.84 to 1.45, I^2 = 0%). Subgroup analysis for the outcome of persistent kidney damage at 3-6 months also showed no significant difference among patients with vesicoureteral reflux (RR 0.99, 95% CI 0.69 to 1.43, I^2 = 0%), as well as among patients without VUR (RR 1.19, 95% CI 0.81 to 1.76, I^2 = 0%).

2-week course versus 3-week course

Cheng et al. evaluated intravenous followed by oral antibiotics given for 2 weeks versus 3 weeks.[26] For both comparisons, antibiotics used depended on sensitivity

and intravenous antibiotics were shifted to oral 2 to 3 days after cessation of fever. No significant difference was observed between a 2-week versus a 3-week antibiotic course in terms of persistence/recurrence of bacteriuria (RR 0.07, 95% CI 0 to 1.19) and recurrence of symptoms or clinical UTI (RR 0.21, 95% CI 0.01 to 4.24).

Route of antibiotics for pediatric pyelonephritis

There were inconclusive results in terms of time to fever resolution, persistent and recurrent UTI, and persistent kidney damage at 3-6 months when only oral antibiotics are given versus intravenous antibiotics followed by oral step-down, and single dose intramuscular antibiotics followed by oral step-down.

Intravenous followed by oral antibiotics versus oral antibiotics only

Four RCTs compared oral antibiotics versus IV antibiotics for 3 to 4 days followed by oral step-down to complete 10-14 days.[27-30] Three studies used third generation cephalosporin,[27-29] while 1 study used ceftriaxone followed by oral co-amoxiclav compared to oral co-amoxiclav.[30] Pooled analysis showed inconclusive results when given oral antibiotics only versus intravenous antibiotics followed by oral antibiotics in terms of time to fever resolution (MD 2.04 days, 95% CI -0.84 to 4.93, I^2 = 0%), persistent UTI at 72 hours (RR 1.10, 95% CI 0.07 to 17.41, I^2 = 0%), and persistent kidney damage at 6-12 months (RR 0.82, 95% CI 0.59 to 1.12, I^2 = 41%). Subgroup analysis of patients with renal parenchymal damage on initial DMSA scan showed no difference between oral antibiotics only versus IV followed by oral antibiotics in terms of persistent kidney damage at 3-6 months (RR 0.79, 95% CI 0.61 to 1.03, I^2 = 19%). Likewise, no significant difference was found in terms of recurrent UTI within 6 months (RR 0.65, 95% CI 0.28 to 1.51).[28]

Single dose intramuscular followed by oral antibiotics versus oral antibiotics only

Baker et al. compared single dose intramuscular ceftriaxone followed by oral TMP-SMX versus TMP-SMX alone for 10 days.[31] Results showed no significant difference in terms of persistent bacteriuria in 48 hours (RR 0.77, 95% CI 0.19 to 3.20) and recurrent UTI within 1 month (RR not estimable).

Antibiotic Regimen for Pediatric Pyelonephritis

Third generation cephalosporins provided significant benefit over other antibiotics in terms of decreased risk for persistent symptoms after end of treatment. No difference was observed between other antibiotic comparisons and outcomes. Microbiologic cure rates are indicated in Table 7.1.

Aminoglycosides

Three studies compared aminoglycosides given once daily versus every 8 hours.[9-11] Two studies used intravenous gentamicin,**[9,10]** while one study used intramuscular netilmicin.[11] Pooled analysis showed inconclusive results in terms of persistent bacteriuria after 1-3 days of treatment (RR 1.05, 95% CI 0.15 to 7.27). No significant difference was found in terms of persistent bacteriuria at 1 week after treatment (RR 2.84, 95% CI 0.12 to 68.57), and reinfection at 1 month after treatment (RR 1.18, 95% CI 0.33 to 4.23).[11] Likewise, no significant difference was also seen between once daily dosing and thrice daily dosing of aminoglycosides in terms of persistence of symptoms at day 3 of IV therapy (RR 1.98, 95% CI 0.37 to 10.53),[9] time to fever resolution (MD 2.40 days, 95% CI -7.90 to 12.70), and kidney parenchymal damage at 3 months (RR 0.74, 95% Ci 0.44 to 1.25).[10]

Cephalosporins

Five studies compared third generation cephalosporins with other antibiotics.[12-16] The study by Schaad et al. compared cefepime (4th generation) with ceftazidime (3rd generation),[17] while Bakkaloglu et al. compared ceftriaxone with cefotaxime.[18] Pooled analysis showed significant benefit for third generation cephalosporins compared to other antibiotics in terms of decreased risk for persistent symptoms after end of treatment (RR 0.28, 95% CI 0.13 to 0.62, I^2 = 38%). Results were inconclusive for outcomes of persistent bacteriuria (RR 1.52, 95% CI 0.53 to 4.35, I^2 = 0%), and recurrence of UTI at end of treatment (RR 1.23, 95% CI 0.32 to 4.74, I^2 = 0%). No difference was found between using third generation cephalosporin and other antibiotics in terms of number of patients with fever for more than 48 hours (RR 5, 95% CI 0.27 to 92.62),[13] as well as recurrent bacteriuria (RR 2.14, 95% CI 0.11 to 40.30) and recurrent symptomatic UTI at end 4-6 weeks (RR not estimatable).[12]

There was no significant difference between cefepime and ceftazidime in terms of persistence or recurrence of initial pathogen at end of IV therapy (RR 3.05, 95% CI 0.13 to 74.16), end of IV and oral therapy (RR 0.12, 95% CI 0.01 to 2.16), at 5-9 days after treatment (RR 2.37, 95% CI 0.47 to 11.91) and at 4-6 weeks after treatment (RR 0.13, 95% CI 0.02 to 1.04). Likewise, no difference was found in terms of infection with a new pathogen at 4-6 weeks post-treatment (RR 1.19, 95% Ci 0.45 to 3.18).[17]

Comparing ceftriaxone versus cefotaxime, no significant difference was found in terms of persistent bacteriuria at 48 hours (RR not estimatable), after 10 days of treatment (RR 0.87, 95% CI 0.37 to 2.03), and UTI at 1 month post treatment (RR 0.68, 95% CI 0.30 to 1.50).[18]

Third generation cephalosporin-beta lactamase inhibitors combination

Two new studies evaluated combined 3rd generation cephalosporin and beta lactamase inhibitors compared to other intravenous antibiotics for pyelonephritis in children.[7,8] Bradley et al. used ceftazidime-avibactam compared to cefepime,[7] while Roilides et al. used ceftolozane-tazobactam compared to meropenem.[8] Pooled analysis showed inconclusive results in terms of favorable clinical response/cure (RR 0.98, 95% CI 0.83 to 1.15, I^2 = 47%) and microbiologic response at 8-15 days from last antibiotics (RR 1.09, 95% CI 0.78 to 1.51, I^2 = 65%). No significant difference was found between ceftazidime-avibactam and cefepime in terms of favorable clinical response at 72 hours of treatment (RR 0.95, 95% CI 0.84 to 1.07) and on late follow-up at 20-36 days post-treatment (RR 0.99, 95% CI 0.79 to 1.24), as well as favorable microbiologic response on late follow-up (RR 1.70, 95% CI 0.64 to 4.54).[7] Meanwhile, no significant difference was found between ceftolozane-tazobactam and meropenem in terms of clinical cure (RR 0.96, 95% CI 0.88 to 1.04) and microbiologic eradication at end of treatment (RR 0.97, 95% CI 0.87 to 1.08).[8]

Table 7.1 Microbiological cure rates.

Antibiotics, route, dose, frequency	Study	%	n	ffup
Co-amoxiclav 100mg/kg/day IV QID 7 days; 50mg/kg/day TID PO	Fischbach 1989; Toporovski 1992	100%	10/10	2-3 days
Netilmicin 5mg/kg/day IV TID 10 days	Vigano 1992	100%	70/70	7 days
Netilmicin 5mg/kg/day IV OD 10 days	Vigano 1992	98.60%	73/74	7 days
Meropenem 20mg/kg/dose IV TID 3 days	Roilides 2023	95.80%	23/24	2 days

Ceftazidime 50 mg/kg/dose IV TID until afebrile	Schaad 1998	94.20%	113/120	10 days
Ceftolozane/Tazobactam 20mg/10mg/kg/day IV TID 3 days	Roilides 2023	93%	66/71	2 days
Cefepime 50mg/kg/dose IV TID ≥3 days or until afebrile	Schaad 1998; Bradley 2019	92.5%	Schaad: 110/115; Bradley: 14/23	8-15 days
Gentamicin IV TID 4.5 to 7.5mg/kg/day (depending on age) 3-5 days	Carapetis 2001; Chong 2003	88.9%	Carapetis: 59/89; Chong: 84/84	2-3 days
Gentamicin IV OD 4.5 to 7.5mg/kg/day (depending on age) 3-5 days	Carapetis 2001; Chong 2003	88.2%	Carapetis: 58/90; Chong 84/84	2-3 days
Ceftibuten 9mg/kg/day PO OD 10 days	Marild 2009	87.10%	222/255	20 days
Cefotaxime 100mg/kg/day IV BID-QID 14 days	Fischbach 1989; Bakkaloglu 1996	84.2%	Fischbach: 9/10; Bakkaloglu: 41/50	2-10 days
Ceftriaxone 50mg/kg/day IV OD 10 days	Bakkaloglu 1996	84%	42/50	10 days
TMP-SMX 3mg/15mg/kg/dose PO BID 10 days	Marild 2009	80.50%	103/128	20 days
Ceftazidime/Avibactam 20-50mg/5-12.5mg/kg/dose (depending on age and creatinine clearance) IV TID ≥3 days	Bradley 2019	79.60%	43/54	8-15 days

SAFETY OUTCOMES

Adverse events

Adverse events were reported in 16 RCTs. Results were inconclusive between once-daily versus 3 times a day dosing for aminoglycosides in terms of hearing impairment (RR 2.83, 95% CI 0.33 to 24.56) and increased creatinine or nephrotoxicity (RR 0.75, 95% CI 0.20 to 2.82). Results were also inconclusive in terms of gastrointestinal adverse events when 3rd generation cephalosporins were compared to other antibiotics (RR 0.93, 95% CI 0.34 to 2.58). No significant difference was found between cefepime and ceftazidime in terms of overall adverse events (RR 1.12, 95% CI 0.76 to 1.63), drug-related adverse effects (RR 1.41, 95% CI 0.65 to 3.07), gastrointestinal (RR 1.12, 95% CI 0.47 to 2.67), and cutaneous adverse effects (RR 1.51, 95% CI 0.26 to 8.91).[17] Likewise, no significant difference were found between ceftriaxone and cefotaxime in terms of overall adverse events (RR 0.67, 95% CI 0.12 to 3.82), gastrointestinal (RR 2, 95% CI 0.13 to 71.92) and cutaneous adverse events (RR 0.33, 95% CI 0.04 to 3.10).[18] Results were inconclusive in terms of adverse event reported for cephalosporin/beta-lactamase inhibitor combinations compared to other antibiotics (RR 0.98, 95% CI 0.77 to 1.27, I^2 = 41%). The most frequently reported adverse events were gastrointestinal side effects such as diarrhea for all antibiotics. Possible drug-related adverse events to ceftazidime-avibactam include moderate nausea, vomiting and dizziness (n=1), mild diarrhea (n=1), rashes (n=3), and nervous system disorder (n=1).[7] Meanwhile, neutropenia was observed in patients given ceftolozane-tazobactam (n=5).[8]

Serious adverse events

Two RCTs reported serious adverse events.[7,8] Results were inconclusive for cephalosporin/beta-lactamase inhibitor combinations compared to other antibiotics (RR 0.99, 95% CI 0.30 to 3.25, I^2 = 41%). Nervous system disorder occurring 2 days after intravenous infusion of ceftazidime-avibactam was reported as possibly drug-related SAE (n=1).[7]

Table 7.2 shows the comparison of different antibiotic regimens used in acute pyelonephritis in children in terms of benefit, harm, resistance rate to the 3 most common bacterial etiologies, and cost.

Table 7.2. Comparison of antibiotic regimens.

Drug Group	Drug	Duration	Route	Benefit (cure rates)	Harm (adverse events)	Resistance Rate (*E. coli, K pneumonia, Enterococcus spp*)	Cost
Aminoglycosides	Amikacin 15mg/kg/day OD	≥3 days	IV	NA	NA	4.2 to 7.2%	Php 126.48 to 1,710.00
	Netilmicin 5mg/kg/day OD	10 days	IV	100%	Hearing impairment 10% (2/20); Renal impairment 2.7% (2/74)	NA	
	Netilmicin 5mg/kg/day TID	10 days	IV	98.60%	Hearing impairment none (0/12); Renal impairment 2.9% (2/80)	NA	
	Gentamicin 4.5 to 7.5mg/kg/day (depending on age) TID	3-5 days	IV	88.9%	Hearing impairment: Chong none (0/79); Carapetis 2.6% (1/39); Renal impairment: Chong 1.3% (1/79); Carapetis 1.6% (1/64)	14.1 to 25.6%	
	Gentamicin IV 4.5 to 7.5mg/kg/day (depending on age) OD	3-5 days	IV	88.2%	Hearing impairment: Chong none (0/88); Carapetis none (0/33); Renal impairment: Chong 2.5% (2/80); Carapetis 1.9% (1/52)	14.1 to 25.6%	
Penicillin	Ampicillin 100-200mg/kg/day	≥3 days	IV	NA	NA	10 to 93.9%	Php 48 to 648
	Co-amoxiclav 100mg/kg/day (IV); 50mg/kg/day (PO)	7-10 days	IV/PO	100%	Fischbach 30% (3/10), diarrhea	20.5 to 37.3%	Php 215 to 1,560
Cephalosporins	Ceftazidime 50 mg/kg/dose TID	until afebrile	IV	94.20%	7% (10/150)	NA	Php 210.45 to 1,260.00
	Cefuroxime 100mg/kg/day IV or 30mg/kg/day PO	7-10 days	IV/PO	NA	NA	36 to 58.5%	IV: Php 301.47 to 904.41; PO: Php 210 to 1050

	Ceftibuten 9mg/kg/day OD	10 days	PO	87.10%	3% (10/309); Majority GI symptoms	NA	NA
	Cefotaxime 100mg/kg/day BID-QID	14 days	IV	84.2%	Fischbach None (0/10); Bakkaloglu 6% (3/50) skin erruptions	54.80%	Php 693 to 53,280
	Ceftriaxone 50mg/kg/day OD	10 days	IV	84%	4% (2/50); GI and skin erruptions	51.10%	Php 1,104 to 4,416
	Cefepime 50mg/kg/dose TID	≥3 days or until afebtrile	IV	92.5%	Schaad 9% (14/149); Roilides 53.6%	NA	Php 410.31 to 2,646
Cephalosporin/ beta-lactamase inhibitor combination	Ampicillin/Sulbactam 100-200mg/kg/day	7-10 days	IV	NA	NA	13.2 to 14.5%	IV: Php 630 to 7,440; PO: 620.39 to 3,101.95
	Pip/Tazobactam 80-100mg/kg/dose (depending on age)	≥3 days	IV	NA	NA	13.2 to 27.7%	Php 885.00 to 3,540
	Ceftolozane/Tazobactam 20mg/10mg/kg/day TID	3 days	IV	93%	14%	NA	NA
	Ceftazidime/Avibactam 20-50mg/5-12.5mg/kg/dose (depending on age and creatinine clearance) TID	≥3 days	IV	79.60%	53.70%	NA	Php 24,390 to 73,170
Carbapenem	Meropenem 20mg/kg/dose TID	3 days	IV	95.80%	15%	16.70%	Php 1,500 to 7,650
Sulfonamide	TMP-SMX 3mg/15mg/kg/dose BID	10 days	PO	80.50%	5% (7/152); majority GI symptoms	50.6 to 55.2%	Php 1,500 to 7,650
Fluoroquinolones	Ciprofloxacin 30mg/kg/day	7-10 days	IV/PO	NA	NA	34.9 to 87.2%	IV: Php 2,169.00 to 11,597.76; PO: 112 to 160

CERTAINTY OF EVIDENCE

Certainty of evidence was downgraded to very low to low due to inconsistency (moderate to substantial heterogeneity), imprecision (wide confidence intervals), and moderate risk of bias due to lack of reporting of randomization and allocation concealment, lack of blinding, and inadequate follow-up in some studies.

RECOMMENDATIONS FROM OTHER GROUPS

These were the recommendations from other groups. Recommendations from the Philippine Pediatric Society, American Academy of Pediatrics, and Italian Society of Pediatric Nephrology includes all urinary tract infections and were not specific for acute uncomplicated pyelonephritis.

Table 7.3. Summary of recommendations from other groups and agencies.

Group or Agency	Recommendations
Philippine Pediatric Society 2004 [2]	No recommendations on duration and route of antibiotics specific for acute pyelonephritis Suggested intravenous antimicrobials for the treatment of UTI: • Ceftriaxone 75mg/kg every 24 hours • Cefotaxime 150mg/kg/day divided every 6 hours • Ceftazidime 150mg/kg/day divided every 6 hours • Cefazolin 50mg/kg/day divided every 8 hours
American Academy of Pediatrics 2011 [32]	**Duration of antibiotics** The clinician should choose 7 to 14 days as the duration of antimicrobial therapy (evidence quality: B; recommendation). **Route of antibiotics** The clinician should base the choice of route of administration on practical considerations. Initiating treatment orally or parenterally is equally efficacious. **Choice of antibiotics** The clinician should base the choice of agent on local antimicrobial sensitivity patterns (if available) and should adjust the choice according to sensitivity testing of the isolated uropathogen (evidence quality: A; strong recommendation).
NICE Guidelines 2018 [33]	**Route and duration of antibiotics** 7-10 days oral antibiotics course recommended; for intravenous treatment, antibiotics should be reviewed by 48 hours and stepped down to oral, when possible, to complete 10 days duration. **Choice of antibiotics** Choice of oral antibiotics for acute pyelonephritis: • Cephalexin 2-3x a day for 7-10 days • Co-amoxiclav (only if culture susceptible) 3x a day for 7-10 days • Trimethoprim (only if culture susceptible) 2x a day for 14 days • Ciprofloxacin (consider safety issues) 2x a day for 7 days. Choice of intravenous antibiotics for acute pyelonephritis (if unable to take oral or severely unwell): • Co-amoxiclav (only if culture susceptible) 3x a day • Cefuroxime 3-4x a day • Ceftriaxone once a day • Ciprofloxacin (consider safety issues) 2-3x a day.

	• Gentamicin 5-7mg/kg once a day (assessment of renal function required) • Amikacin 15mg/kg once a day (assessment of renal function required)
KHA-CARI guideline Australia 2014 [1]	**Route and duration of antibiotics** Oral antibiotics can be given if patient is a) low risk for serious illness, b) not septic-looking, c) able to tolerate oral medications. Duration of 7-10 days recommended. Single dose therapy not recommended
Italian Society of Pediatric Nephrology 2019 [34]	**Duration of antibiotics** Suggest a 10-day course; parenteral therapy can be limited to 3 days. **Route of antibiotics** • If UTI is complicated, child appears septic or severely dehydrated, vomiting, or concerns with compliance are present, treatment should be started parenterally and continued with oral antibiotic as soon as clinical conditions allow. • If UTI is not complicated, child is in good condition and able to retain oral fluids and medications, and compliance is expected, administer treatment via oral route. **Choice of antibiotics** Base choice on local antimicrobial sensitivity patterns (if available) and adjust it according to sensitivity testing of the isolated uropathogen. Agents excreted in urine but do not achieve therapeutic blood concentrations (e.g., nitrofurantoin) should NOT be used to treat febrile UTI (insufficient to treat pyelonephritis)

ONGOING STUDIES AND RESEARCH GAPS

There is an ongoing study on acute pyelonephritis in children in terms of duration of antibiotics using ceftriaxone and amikacin as 3-day intravenous medication versus 3 days IV followed by 7 days oral co-amoxiclav step-down.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Local resistance pattern of intravenous and oral antibiotics

The 2021 Antimicrobial Resistance Surveillance Program (ARSP) showed that *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter* sp. as the top three most common organisms isolated from urine cultures.[35] Table 7.4 shows the local resistance rates of *E. coli* urine isolates to intravenous antibiotics, with most susceptibility to amikacin (4.2%) and most resistant to ciprofloxacin (53.7%). *K. pneumoniae* urine isolates (Table 7.6) showed higher resistance patterns, with colistin being the least resistant (6.5%), and cephalosporins and ciprofloxacin being the most resistant (26.7-58.5%). Meanwhile, *E. faecalis* urine isolates are least resistant to linezolid (2.8%) and most resistant to ciprofloxacin (34.9%) (Table 7.8). For *E. faecium* (Table 7.10), least resistance was observed for linezolid (4%), while highest resistance was observed for penicillin (95%). For oral antibiotics, Table 7.5 shows the local resistance rates of *E. coli* urine isolates to oral antibiotics, with most susceptibility to ampicillin-sulbactam (14.5%) and most resistant to co-trimoxazole (55.2%). *K. pneumoniae* urine isolates

(Table 7.7) showed higher resistance patterns for common oral antibiotics, being most susceptible to co-amoxiclav (37.3%) and most resistant to cefuroxime (58.5%). *E. faecalis* (Table 7.9) is most susceptible to ciprofloxacin (34.9%) but *E. faecium* (Table 7.11) shows the highest resistance to the same antibiotic (87.2%).

Table 7.4. Resistance rates of *E. coli* urine isolates to intravenous antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Amikacin (n=2,137)	4.2%
Ertapenem (n=1,959)	5.6%
Pip/Tazobactam (n=2,174)	13.2%
Ampicillin-Sulbactam (n=880)	27.4%
Cefuroxime (n=75)	36%
Ceftriaxone (n=2,201)	40.3%
Cefazolin (n=1,175)	45.4%
Ciprofloxacin (n=2,188)	53.7%

Table 7.5. Resistance rates of *E. coli* urine isolates to oral antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Ampicillin Sulbactam (n=165)	14.5%
Amoxicillin Clavulanic (n=616)	20.5%
Cefuroxime (n=58)	39.7%
Ciprofloxacin (n=617)	48.9%
Co-trimoxazole (n=616)	55.2%

Table 7.6. Resistance rates of *K. pneumoniae* to intravenous antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Colistin (n=430)	6.5%
Amikacin (n=1,479	7.2%
Ertapenem (n=1,364)	12.3%
Imipenem (n=1,532)	16.1%
Meropenem (n=1,493)	16.7%
Gentamicin (n=1,504)	23.8%
Cefoxitin (n=1,520)	26.7%
Pip/Tazobactam (n=1,509)	27.9%
Cefepime (n=1,512)	35.6%
Ceftriaxone (n=1,520)	51.1%
Cefotaxime (n=871)	54.8%
Cefazolin (n=860)	55.2%
Ciprofloxacin (n=1,525)	55.2%
Cefuroxime (n=728)	58.5%

Table 7.7. Resistance rates of *K. pneumoniae* urine isolates to oral antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Amoxicillin Clavulanic (n=1,512)	37.3%
Co-trimoxazole (n=1,532)	50.6%
Ciprofloxacin (n=1,525)	55.2%
Cefuroxime (n=728)	58.5%

Table 7.8. Resistance rates of *E. faecalis* urine isolates to intravenous antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Linezolid (n=727)	2.8%
Vancomycin (n=840)	3.2%

Ampicillin (n=827)	10%
Gentamicin, high level (n=660)	14.1%
Penicillin G (n=805)	21.1%
Ciprofloxacin (n=764)	34.9%

Table 7.9. Resistance rates of *E. faecalis* urine isolates to oral antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Ciprofloxacin (764)	34.9%
Tetracycline (n=704)	77.3%

Table 7.10. Resistance rates of *E. faecium* to intravenous antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Linezolid (n=753)	4%
Gentamicin, high level (n=633)	25.6%
Vancomycin (n=788)	30.8%
Ciprofloxacin (n=704)	87.2%
Ampicillin (n=740)	93.9%
Penicillin (701)	95%

Table 7.11. Resistance rates of *E. faecium* urine isolates to oral antibiotics (Source: ARSP 2021).

Drugs	% Resistance
Tetracycline (n=683)	38.9%
Ciprofloxacin (n=704)	87.2%

Cost

No evidence regarding the cost-effectiveness of antibiotics for the treatment of acute pyelonephritis were found. The following are the recommended doses and cost of intravenous and oral antibiotics:

Table 7.12. Cost of intravenous antibiotics.

Drugs	Dose[36]	Cost per tab/solution[37,38]	Cost for a 3-day regimen*
Aminoglycosides	15mg/kg Q24 (max dose 1.5g)	50 mg/mL, 2 mL Php 89.00 125 mg/mL, 2 mL Php 42.16 250 mg/mL, 2 mL Php 95.00	Php 126.48 to 1,710.00
Ampicillin-sulbactam	100-200 mg/kg/24 hr divided into Q6 hr (Max dose: 2g ampicillin/dose)	1g + 500mg/vial Php 310.00 500mg + 250mg/vial Php 210.00	Php 630 to 7,440
Ampicillin	100-200 mg/kg/24 hr divided Q6 hours; max dose: 8 g/24 hr	1g/vial Php 48.00 250mg/vial Php 54.00	Php 48 to 648
Cefepime	100 mg/kg/24 hr divided into Q12 hr (Max. dose: 4 g/24 hr)	500mg/vial Php 136.77 1g/vial	Php 410.31 to 2,646

		Php 312.50 2g/vial Php 441.10	
Ceftazidime	100e150 mg/kg/24 hr divided into Q8 hr; max. dose: 6g/24 hr	500mg/vial 70.15 1g/vial 210.00	Php 210.45 to 1,260.00
Ceftazidime/avibactam	≥3 mo to <6 mo: 40 mg/kg/dose IV Q8 hr ≥6 mo, child, and adolescent: 50 mg/kg/dose IV Q8 hr (max. 2 g/dose)	2g/500ml Php 8,130	Php 24,390 to 73,170
Ceftriaxone	100 mg/kg/24 hr divided into Q12 hr (Max. dose: 2 g/dose and 4 g/24 hr)	1g/vial Php 368.00	Php 1,104 to 4,416
Cefotaxime	100-200 mg/kg/24 hr divided into Q6-8 hr; max dose: 12g/24h	500mg/vial Php 740.00 250mg/vial Php 77.00	Php 693 to 53,280
Cefuroxime	100 mg/kg/24 hr divided into Q8 hr (Max. dose: 1500 mg/dose)	1.5g/vial Php 100.49	Php 301.47 to 904.41
Meropenem	20mg/kg/dose Q8 (max dose: 1g/dose)	1g/vial Php 850.00 500mg/vial Php 550.00	Php 1,500 to 7,650
Piperacillin-tazobactam	2-9 mo: 80 mg/kg/dose IV Q6 hr >9 mo, child, and adolescent: 100 mg/kg/dose (max. 4000 mg/dose) IV Q6 hr (Max dose: 16 g/24 hr)	2 g + 250 mg/vial Php 310.00 4g + 500mg/vial Php 295.00	Php 885.00 to 3,540
Ciprofloxacin	18-30 mg/kg/24 hr divided Q8 hr; max. dose: 1.2 g/24 hr	2mg/ml 100ml/vial Php 241.08 2mg/ml, 200ml/vial Php 1,306.64	Php 2,169.00 to 11,597.76

*Depending on patient's weight, maximum dose per day

Table 7.13. Cost of oral antibiotics.

Drugs	Dose[36]	Cost per tab/solution[37,38]	Cost for a 7-day regimen	Cost for a 10-day regimen
Sultamicillin (oral ampicillin sulbactam)	<30 kg 25-50mg/kg/day in two divided doses ≥30kg 375-750 mg orally twice daily.	Php 620.39 per 250mg/5ml 60ml bottle Php 93.7/375mg tab	Syrup: Php 620.39 to 2,481.56 (1-4 bottles) Tablet: Php 1,312 to 1,628	Syrup: 620.39 to 3,101.95 (1-5 bottles) Tablet: Php 1,874 to 2,326

		Php 116.3/750mg tab		
Amoxicillin Clavulanic	Infant 1≤3 mo: 30 mg/kg/24 hr O Q12 hr PO Child ≥3 mo: <40 kg: TID dosing: 20-40 mg/kg/24 hr Q8 hr PO BID dosing: 25-45 mg/kg/24 hr O Q12 hr PO ≥40 kg: 250-500 mg/dose Q8 hr PO	200mg/28.5mg/5ml Php 215.00 400mg/57mg/5ml Php 312.00 600mg/42.9mg/5ml Php 279.99 500mg/125mg tab Php 19.00	Syrup: Php 215 to 1,248 (1-4 bottles) Tablet: Php 399.00	Syrup: Php 215 to 1,560 (1-5 bottles) Tablet: Php 570.00
Cefuroxime	30 mg/kg/day divided Q12 hr; max. dose: 1 g/24 hr	125 mg/5 mL Php 210.00 250mg/5ml Php 210.00 500mg/tab Php 44.00	Syrup: Php 210 to 840 (1-4 bottles) Tablet: Php 616.00	Syrup: Php 210 to 1050 (1-5 bottles) Tablet: Php 880.00
Co-trimoxazole	8-12 mg/kg/24 hr divided BID; max. dose: 160 mg/dose	400mg/80mg/5ml Php 350 400mg/80mg/tab Php 1.26 800mg/160mg/tab Php 3.90	Syrup: Php 350 to 1400 (1-4 bottles) Tablet: Php 17.64 to 54.6	Syrup: Php 350 to 1750 (1-5 bottles) Tablet: Php 24.8 to 78
Ciprofloxacin	20-40 mg/kg/24 hr divided Q12 hr; max. dose: 1.5 g/24 hr	500mg/tab Php 8.00	Php 112	Php 160

Patient's values and preference, equity, acceptability, and feasibility

No studies exploring intravenous antibiotics preference and acceptability in children were found.

REFERENCES

1. McTaggart S, Danchin M, Ditchfield M, Hewitt I, Kausman J, Kennedy S, et al. (Kidney Health Australia – Caring for Australasians with Renal Impairment). KHA-CARI guideline: Diagnosis and treatment of urinary tract infection in children. Nephrology (Carlton). 2015; 20(2): 55-60.
2. Philippine Pediatric Society. Clinical practice guidelines in the approach and treatment of urinary tract infection in children in the Philippines. 2004. PPS
3. Bay A, Anacleto F. Clinical and laboratory profile of urinary tract infection among children at the outpatient clinic of a tertiary hospital. Pediatric Infectious Disease Society of the Philippines Journal. 2010; 11(1): 10-16
4. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. Pediatrics. 2010;126(6):1084-91.
5. Pleniceanu O, Twig G, Tzur D, Sherman G, Afek A, Erlich T, et al. Acute pyelonephritis in children and the risk of end-stage kidney disease. J Nephrol. 2021;34(5):1757-1765.
6. Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev. 2014;(7):CD003772

7. Bradley JS, Roilides E, Broadhurst H, Cheng K, Huang LM, MasCasullo V, et al. Safety and Efficacy of Ceftazidime-Avibactam in the Treatment of Children ≥3 Months to <18 Years With Complicated Urinary Tract Infection: Results from a Phase 2 Randomized, Controlled Trial. Pediatr Infect Dis J. 2019;38(9):920-928
8. Roilides E, Ashouri N, Bradley JS, Johnson MG, Lonchar J, Su FH, et al. Safety and Efficacy of Ceftolozane/Tazobactam Versus Meropenem in Neonates and Children With Complicated Urinary Tract Infection, Including Pyelonephritis: A Phase 2, Randomized Clinical Trial. Pediatr Infect Dis J. 2023;42(4):292-298.
9. Carapetis JR, Jaquiery AL, Buttery JP, Starr M, Cranswick NE, Kohn S, et al. Randomized, controlled trial comparing once daily and three times daily gentamicin in children with urinary tract infections. Pediatr Infect Dis J. 2001;20(3):240-6
10. Chong CY, Tan AS, Ng W, Tan-Kendrick A, Balakrishnan A, Chao SM. Treatment of urinary tract infection with gentamicin once or three times daily. Acta Paediatr. 2003;92(3):291-6.
11. Viganò A, Principi N, Brivio L, Tommasi P, Stasi P, Villa AD. Comparison of 5 milligrams of netilmicin per kilogram of body weight once daily versus 2 milligrams per kilogram thrice daily for treatment of gram-negative pyelonephritis in children. Antimicrob Agents Chemother. 1992;36(7):1499-503.
12. Banfi AG, Hill-Juarez JM, Kaufman A, Moens E. Multinational comparative trial of ceftibuten and trimethoprim-sulfamethoxazole in the treatment of children with complicated or recurrent urinary tract infections. Members of the ceftibuten urinary tract infection international study group. Pediatric Infectious Disease Journal 1993;12(6 Suppl):S84–S91.
13. Fischbach M, Simeoni U, Mengus L, Jehl F, Monteil H, Geisert J, et al. Urinary tract infections with tissue penetration in children: cefotaxime compared with amoxycillin/clavulanate. J Antimicrob Chemother. 1989;24 Suppl B:177-83
14. Mårild S, Jodal U, Sandberg T. Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. Pediatr Nephrol. 2009;24(3):521-6
15. Noorbakhsh S, Lari AR, Masjedian F, Mostafavi H, Alaghehbandan R. Comparison of intravenous aminoglycoside therapy with switch therapy to cefixime in urinary tract infections. Saudi Med J. 2004;25(10):1513-5.
16. Toporovski J, Steffens L, Noack M, Kranz A, Burdeska A, Kissling M. Effectiveness of cefetamet pivoxil in the treatment of pyelonephritis in children. J Int Med Res. 1992;20(1):87-93.
17. Schaad UB, Eskola J, Kafetzis D, Fishbach M, Ashkenazi S, Syriopoulou V, et al. Cefepine vs. ceftazidime treatment of pyelonephritis: a European, randomized, controlled study of 300 pediatric cases. European Society for Paediatric Infectious Diseases (ESPID) Pyelonephritis Study Group. Pediatr Infect Dis J. 1998;17(7):639-44
18. Bakkaloglu A, Saatci U, Soylemezoglu O, Ozen S, Topaloglu R, Besbas N, et al. Comparison of ceftriaxone versus cefotaxime for childhood upper urinary tract infections. J Chemother. 1996;8(1):59-62
19. Grimwood K, Abbott GD, Fergusson DM. Single dose gentamicin treatment of urinary infections in children. N Z Med J. 1988;101(852):539-41
20. Repetto HA, MacLoughlin GJ. Single-dose cefotaxime in the treatment of urinary tract infections in children: a randomized clinical trial. J Antimicrob Chemother. 1984;14 Suppl B:307-10.
21. Benador D, Neuhaus TJ, Papazyan JP, Willi UV, Engel-Bicik I, Nadal D, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. Arch Dis Child. 2001;84(3):241-6
22. Vilaichone A, Watana D, Chaiwatanarat T. Oral ceftibuten switch therapy for acute pyelonephritis in children. J Med Assoc Thai. 2001;84 Suppl 1:S61-7.
23. Bouissou F, Munzer C, Decramer S, Roussel B, Novo R, Morin D, et al. Prospective, randomized trial comparing short and long intravenous antibiotic treatment of acute pyelonephritis in children: dimercaptosuccinic acid scintigraphic evaluation at 9 months. Pediatrics 2008;121 (3):e553–60.
24. Francois P, Bensman A, Begue P, Artaz M-A, Coudeville L, Lebrun T, et al. Assessment of the efficacy and cost efficiency of two strategies in the treatment of acute pyelonephritis in children: oral cefixime or parenteral ceftriaxone after an initial IV combination therapy [Evaluation de l'efficacité et du coût de deux stratégies thérapeutiques dans les pyélonéphrites de l'enfant: céfixime per os versus ceftriaxone parentérale en relais d'une bithérapie intraveineuse]. Medecine et Maladies Infectieuses 1997;27(Spec Iss June): 667–73.
25. Levtchenko E, Lahy C, Levy J, Ham H, Piepsz A. Treatment of children with acute pyelonephritis: a prospective randomized study. Pediatr Nephrol. 2001;16(11):878-84
26. Cheng CH, Tsau YK, Lin TY. Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia. Pediatrics. 2006;117(1):e84-9.

27. Bocquet N, Sergent Alaoui A, Jais JP, Gajdos V, Guigonis V, Lacour B, et al. Randomized trial of oral versus sequential IV/oral antibiotic for acute pyelonephritis in children. Pediatrics. 2012;129(2):e269-75.
28. Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics. 1999;104(1 Pt 1):79-86
29. Neuhaus TJ, Berger C, Buechner K, Parvex P, Bischoff G, Goetschel P, et al. Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. Eur J Pediatr. 2008;167(9):1037-47.
30. Montini G, Toffolo A, Zucchetta P, Dall'Amico R, Gobber D, Calderan A, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. BMJ. 2007;335(7616):386.
31. Baker PC, Nelson DS, Schunk JE. The addition of ceftriaxone to oral therapy does not improve outcome in febrile children with urinary tract infections. Arch Pediatr Adolesc Med. 2001;155(2):135-9
32. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management; Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011 Sep;128(3):595-610
33. National Institute for Health and Care Excellence. NICE Guidelines: Urinary tract infection in under 16s: diagnosis and management. 2018. Accessed from: www.nice.org.uk/guidance/ng111
34. Ammenti A, Alberici I, Brugnara M, Chimenz R, Guarino S, La Manna A, et al. Italian Society of Pediatric Nephrology. Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatr. 2020;109(2):236-247.
35. Department of Health, Research Institute for Tropical Medicine. Antimicrobial resistance surveillance program annual summary 2021. Accessed from https://arsp.com.ph
36. Anderson CC, Kapoor S, Mark TE (eds). The Harriet Lane Handbook. 23rd edition. PA: Elsevier; 2024
37. Department of Health. Drug Price Reference Index 2022 10th edition. Available from: https://dpri.doh.gov.ph. Accessed: July 5, 2023.
38. Southstar Drug. Available from: https://southstardrug.com.ph/. Accessed: July 5, 2023

Management of Recurrent UTI

Question 8. Among adult patients with recurrent UTI, should we recommend giving antibiotics as prophylaxis?

Recommendations

Among adult women with recurrent UTI, we **suggest** the use of antibiotic prophylaxis after maximizing all other preventive measures ***(Low certainty of evidence, Weak recommendation)***

Footnote:

- *Review local and institutional antibiograms, if available.*
- *Some antibiotics that have been used for prophylaxis are as follows:*
    - *Fosfomycin 3g sachet, 1 sachet every 10 days*
    - *Nitrofurantoin 100 mg tab, 1 tab ODHS*
    - *Cefalexin 250 mg cap, 1 cap OD*
    - *Norfloxacin 200 mg tab OD*
    - *Trimethoprim-sulfamethoxazole 40mg/200mg cap, 1 cap ODHS*

Consensus Issues

- Due to the concern regarding multi-drug resistance, effects of long-term antibiotics, and availability of drugs used in the studies, the panel suggested the use of alternative strategies as the primary measure for preventing recurrent UTI. Some examples of preventive measures are the use of cranberry products, probiotics, lifestyle changes, and comprehensive work up as to determine the cause of recurrences.
- The panel emphasized addressing risk factors, underlying causes, and the patient's health status to decrease the risk of recurrence of UTI without the need for drugs.

KEY FINDINGS

Eleven randomized controlled trials with 747 participants were included in this review. They investigated the efficacy and safety of antibiotics compared to placebo as prophylaxis for recurrent UTI in women. No study was identified having men in the population. Antibiotics significantly decreased the risk of clinical and microbiologic recurrence of UTI (clinical recurrence RR 0.14, 95% CI 0.08-0.27; microbiological recurrence RR 0.14 95% CI 0.1-0.2) during prophylaxis. Antibiotics also significantly decreased the risk of microbiologic recurrence after the prophylaxis period (RR 0.71, 95% CI 0.59-0.84). There were no significant differences between antibiotics and placebo in terms of severe side effects (RR 1.63, 95% CI 0.61-4.22) and other side effects (RR 1.8896, 95% CI 1.12-3.175). Most studies lacked information about the randomization process and allocation concealment. The overall certainty of evidence is low due to serious risk of bias, imprecision, and inconsistency.

INTRODUCTION

Recurrent urinary tract infection (UTI) is defined as 2 or more UTIs in 6 months or 3 or more UTIs in 12 months.[1] It is due to persistent bacterial infection or a reinfection.[1] The estimated burden of recurrent UTI is 1 in 4 women will have a recurrence within a year.[1] Recurrent UTI can cause significant discomfort and distress on a patient's

life hence some preventive options have been given to patients including antibiotic prophylaxis. Due to the growing concern about antimicrobial resistance, it is important to know if antibiotic prophylaxis will result to significantly more benefits than harm.

The Philippine CPG in 2015 recommended antibiotic prophylaxis in women whose frequency of recurrence is not tolerated by the patient. Prophylaxis should be limited to women whom non-antimicrobial strategies have not been effective. Prophylaxis can either be given continuously for 6 to 12 months, intermittently, or post-coitally.[1]

This review aims to give an update to the previous recommendations. It aims to evaluate the efficacy and safety of antibiotic prophylaxis for recurrent uncomplicated UTI in adults.

REVIEW METHODS

A literature search was conducted for studies published in the last 10 years, from 2013 to January 5, 2023. Studies found in this search were added to the evidence base of the 2015 guidelines. The inclusion criteria were: (1) adult patients with recurrent uncomplicated UTI; (2) treatment was antibiotic prophylaxis; (3) comparator was either placebo or no antibiotic prophylaxis; (4) randomized controlled studies, systematic review or clinical practice guidelines; (5) outcomes studied were prevention of recurrent UTI, resolution of recurrent UTI, improvement of symptoms, progression of symptoms, complications, morbidity, adverse events, drug-drug interactions, and cost.

Excluded studies were: (1) patients were children; (2) patients with complicated UTI; (3) observational studies such as cohort or case-control studies; (4) studies with no available English translation.

Databases searched were Pubmed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, ChinaXiv, MedRxiv, and BioRxiv. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, Chinese Clinical Trial registry, World Health Organization International Clinical Trials Registry Platform, and EU Clinical trials register). A combined MeSH and free text search were done using the following terms: antibiotic, recurrent, urinary tract infection, and adult. References of all studies were reviewed to identify other studies. Searches were limited to human studies.

RESULTS

Of the 386 records identified from the search, there were 8 clinical practice guidelines, 5 systematic reviews, 11 randomized controlled trials (RCT), and 1 unpublished but completed trial were found. A total of 747 patients included in these RCTs. The previous Philippine CPG on UTI 2015 drew its recommendations based on the Cochrane Review by Albert et al. in 2004, which analyzed 10 RCTs studying antibiotics versus placebo for recurrent UTI.[1,2] Since then, only 1 new RCT by Rudenko et al. (2005) has been added studying the efficacy of fosfomycin prophylaxis for recurrent UTI.[3]

Characteristics Of included studies

The review by Albert et al. analyzed 10 double-blind RCTs comparing the efficacy of antibiotics versus placebo in reducing the UTI recurrence in women with history of 2

or 3 episodes of UTI within the last 6 or 12 months. The women involved were mostly adults, with ages ranging from 18 to 77 years old. One RCT included adults and adolescents 12 years old and above. The setting was mainly clinics for most RCTs. Various antibiotics were used by the RCTs such as cinoxacin, cephalexin, nitrofurantoin, norfloxacin, and TMP-SMX. Different doses for cinoxacin (250 mg and 500 mg) and nitrofurantoin (50 mg and 100 mg) were used. The duration of treatment also varied from 6 to 12 months. The control was placebo in all studies. Outcomes measured were number of bacteriuric episodes, % patients with no recurrence, % patients with at least one microbiologic recurrence during and after prophylaxis, % patients with at least one clinical recurrence during prophylaxis, organisms isolated in bacteriuric episodes, and time to infection after intervention. Some studies did not have follow-up while some studies had a follow-up until 12 months after intervention. The characteristics of included studies are summarized in Appendix 5: Appendix Table 5.8.[2]

The study by Rudenko et al. (2005) is a double-blind, randomized, placebo-controlled trial done in Ukraine involving 317 non-pregnant women with recurrent UTI. Patients were randomized to receive either 3 g of Fosfomycin or placebo for 6 months. The outcomes studied were (1) number of UTI recurrences during the prophylaxis period, (2) number of UTI recurrences during post-prophylaxis period of 6 months, (3) number of patients with UTI recurrence, (4) time to first recurrence of UTI since randomization, (4) treatment compliance, and (5) adverse events.[3]

Efficacy outcomes

When pooling the studies from Albert et al. (2004) and Rudenko et al. (2005) together, 11 RCTs showed a significantly decreased risk of at least one microbiological recurrence of UTI during prophylaxis (RR 0.14, 95% CI 0.1-0.2) with moderate certainty of evidence. Seven RCTs showed a significantly decreased risk of at least one clinical recurrence during prophylaxis (RR 0.14, 95% CI 0.08-0.26) with moderate certainty of evidence. Three RCTs studied patient outcomes after prophylaxis and noted decreased risk of at least one microbiological recurrence during the post-prophylaxis period (RR 0.71, 95% CI 0.59-0.84). For this, the certainty of evidence was low.[2,3]

Safety outcomes

When pooling the results of the 11 RCTs, there was no significant difference in risk of severe side effects (RR 1.6377, 95% CI 0.631-4.225.13) with very low certainty of evidence. Ten RCTs showed increased risk of non-severe side effects (RR 1.8896, 95% CI 1.12-3.175) with moderate very low certainty of evidence. Severe side effects were defined as events requiring withdrawal of patients from treatment. The most common severe side effect was rash. Other less frequent severe side effects were dizziness, abdominal pain, anorexia, vomiting, diarrhea, and elevated AST. For side effects not requiring withdrawal of treatment, the most common was vaginitis and insomnia.[2,3]

Table 8.1. GRADE Summary Findings.

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with antibiotic prophylaxis
patients with at least one microbiological recurrence during prophylaxis	674 (11 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 0.14** (0.10 to 0.20)	698 per 1,000	**600 fewer per 1,000** (628 fewer to 558 fewer)
patients with at least one clinical recurrence during prophylaxis	257 (7 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 0.14** (0.08 to 0.26)	512 per 1,000	**441 fewer per 1,000** (471 fewer to 379 fewer)
patients with at least one microbiological recurrence after prophylaxis	372 (3 RCTs)	⊕⊕◯◯ Low[a,b]	**RR 0.71** (0.59 to 0.84)	694 per 1,000	**201 fewer per 1,000** (285 fewer to 111 fewer)
severe side effects	722 (11 RCTs)	⊕⊕◯◯ Low[a,c]	**RR 1.63** (0.63 to 4.22)	15 per 1,000	**9 more per 1,000** (5 fewer to 47 more)
other side effects	420 (10 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 1.88** (1.12 to 3.17)	77 per 1,000	**68 more per 1,000** (9 more to 167 more)

EXPLANATION

a. Most studies did not provide information regarding the method of randomization and allocation concealment. Many studies also did not have follow-up period after intervention.
b. Some studies show significant benefit while other studies show no significant difference.
c. The number of events is low and there is a wide confidence interval.

CERTAINTY OF EVIDENCE

The RCT by Rudenko et al. was noted to have low risk of bias. The review by Albert et al. was appraised using the AMSTAR 2 tool. Generally, the review had good quality except for few missing information. The authors did not report the sources of funding for the individual RCTs. The heterogeneity of the RCTs was not discussed and explained. Publication bias was not adequately investigated. It must be noted that most of the RCTs included in the review were studies done in the 1970's and 1980's, and some of these information may not have been routinely reported during that time. Due to lack of these information, the RCTs were judged to have serious risk of bias as reflected in the GRADE Evidence Profile. For efficacy outcomes, there was serious risk of inconsistency aside from serious risk of bias. For safety outcomes, there was serious risk of bias and serious imprecision. Hence, the overall certainty of evidence was rated to be low.

RECOMMENDATIONS FROM OTHER GROUPS

Table 8.2. Summary of recommendations from other groups.

Group	Recommendation
American Urologic Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) 2022 [4]	Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. (Conditional Recommendation; Evidence Level: Grade B)
National Institute for Health and Care Excellence (NICE) 2018 [5]	For women with recurrent UTI who are not pregnant, consider a trial of antibiotic prophylaxis only if behavioral and personal hygiene measures, and vaginal estrogen (in postmenopausal women) are not effective or not appropriate.
Infectious Diseases Society of America	No recommendation
World Health Organization 2021 [6]	Antibiotic prophylaxis is only recommended to prevent recurrent urinary tract infections in pregnant women in the context of rigorous research.

ONGOING STUDIES AND RESEARCH GAPS

There are no ongoing trials. There is lack of studies about the efficacy of other antibiotics in the Philippines used for urinary tract infection such as ofloxacin, ciprofloxacin, amoxicillin-clavulanic acid, cefixime, cefuroxime and amoxicillin.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Local resistance pattern of oral antibiotics

Based on the data on antimicrobial resistance surveillance in the Philippines from 2017 to 2021, there is high resistance of common UTI organisms to trimethoprim-sulfamethoxazole and ciprofloxacin. There is relatively low resistance to nitrofurantoin. No data is available for fosfomycin, cefalexin, and norfloxacin. Cinoxacin is already an obsolete drug and therefore, has no data available.

Table 8.3. Oral antibiotics *E-coli* resistance rate in urine isolates of out-patients (ARSP, 2021).[7]

Drugs	% Resistance
Nitrofurantoin (n=373)	5.9%
Ampicillin Sulbactam (n=165)	14.5%
Amoxicillin Clavulanic (n=616)	20.5%
Cefuroxime (n=58)	39.7%

Ciprofloxacin (n=617)	48.9%
Co-trimoxazole (n=616)	55.2%

Cost

A cost-effectiveness study done by Stamm et al. in 1981 showed that the direct costs of 1 year of antibiotic prophylaxis, using TMP-SMX, in a patient approximate those of treating one episode of cystitis.[8] This means that for women with recurrent UTI, it is cost effective to have prophylaxis. Another study by Eells et al. in 2014 compared 5 different strategies in preventing recurrent UTI in women, including daily nitrofurantoin prophylaxis, daily estrogen prophylaxis, daily cranberry prophylaxis, acupuncture prophylaxis and symptomatic self-treatment.[8] This study showed that nitrofurantoin prophylaxis was the most effective strategy in reducing UTI rate but was also the most expensive costing $821 per year.[9] Both studies were done in the United States of America.

No cost-effectiveness studies are available in the Philippines. Table 8.3 shows the cost of generic antibiotics per piece and for the whole treatment period, assuming 6 months of duration. [10,11,12]

Table 8.4. Projected costs of antibiotic prophylaxis for 6 months.

Antibiotic	Price per piece	Price for treatment period
Trimethoprim-sulfamethoxazole 40 mg/200 mg cap, 1 cap ODHS	40mg/200mg cap not available 40mg/200mg/5ml suspension P90/bottle of 60ml	P1,350
Fosfomycin 3 g sachet, 1 sachet every 10 days	P 412.5/sachet	P 7,425
Nitrofurantoin 100 mg tab 1 tab ODHS	P 69.14	P12,445
Cefalexin 250 mg cap, 1 cap OD	P 14.5	P 5,175
Norfloxacin 200 mg tab OD	200 mg tab not available 400 mg tab P4/tab	P360

Patient's values and preference, equity, acceptability, and feasibility

No studies are available about the patient's values, preference, equity, acceptability and feasibility.

REFERENCES

1. Philippine Society for Microbiology and Infectious Diseases. Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infections in Adults 2015 Update: Part 2 [Internet]. 2015 [cited 2023 Mar 3]. Available from https://www.psmid.org/diagnosis-and-management-of-urinary-tract-infections-in-adults-2015-update-part-2/
2. Albert X, Huertas I, Pereiro, I, et al. Antibiotics for preventing recurrent urinary tract infections in non-pregnant women. Cochrane Database of Systematic Reviews [Internet]. 2004 [cited 2023 Mar 3]; Issue 3. Art No.:CD001209. Available from: doi:10.1002/14651858.CD001209.pub2/full

3. Rudenko, N and Dorofeyev. Prevention of Recurrent Lower Urinary Tract Infections by Long-term Administration of Fosfomycin Trometamol. Arzneim.-Forsch./Drug Res. 2005; 55(7):420-427.
4. Anger J, Lee U, Ackerman AL, Chou R, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol. 2019 Aug; 202(2):282-289. doi: 10.1097/JU.0000000000000296. Epub 2019 Jul 8. Update in: J Urol. 2022 Oct;208(4):754-756. PMID: 31042112.
5. National Institute for Health and Care Excellence. Urinary tract infection (recurrent): antimicrobial prescribing [Internet]. [London]: NICE; 2018 [cited 2023 Mar 3]. NICE guideline [NG112]. Available from: https://www.nice.org.uk/guidance/ng112.
6. World Health Organization. WHO recommendation on antibiotic prophylaxis to prevent recurrent urinary tract infections [Internet]. 29 Aug 2021 [cited 2023 Mar 3]. Available from https://srhr.org/rhl/article/who-recommendation-on-antibiotic-prophylaxis-to-prevent-recurrent-urinary-tract-infections#:~:text=A%20recurrent%20urinary%20tract%20infection,UTI)%2C%20generally%20after%20treatment.
7. Antimicrobial Resistance Surveillance Program Annual Report - 2021. Manila: Antimicrobial Resistance Surveillance Program; 2022.
8. Stamm WE, McKevitt M, Counts GW, et al. Is Antimicrobial Prophylaxis of Urinary Tract Infections Cost Effective? Annals of Internal Medicine. 1981;94:251-255.
9. Eells, SJ, Bharadwa K, McKinnell, et al. Recurrent Urinary Tract Infections Among Women: Comparative Effectiveness of 5 Prevention and Management Strategies Using a Markov Chain Monte Carlo Model. Clinical Infectious Diseases 2014;58(2):147-60.
10. MIMS Philippines [Mobile application software]. Version. 3.2.0. Philippines: MIMS Pte Ltd. (2023).
11. Department of Health (DOH) Pharmaceutical Division. Drug Price Reference Index (DPRI) 2022 10th Edition. Philippines. Accessed 8 Mar 2023. Available from: https://dpri.doh.gov.ph
12. Philippine Pharmaceutical Directory (PPD) Clinic [Mobile application software]. Version 3.16.1. Philippines:Medicomm Pacific, Inc. (2023).

Question 9. Among patients with recurrent UTI, should we recommend cranberry as a preventive measure?

Recommendations

Among women with recurrent UTI, we **suggest** cranberry products ***(Low certainty of evidence, Weak recommendation)***

Consensus Issues

- The panel noted that the available evidence on cranberry for prophylaxis against UTI is limited on recurrent UTI population, thus the recommendation for its use is limited to this population only. Further research is required to extend its use in the general population.
- Cranberry products should not replace standard antibiotic treatment for active UTI, as panel emphasized that antibiotics are still the primary treatment for ongoing infection.
- Since the studies are based on international setting, panel proposed additional research is needed especially in local setting.
- The panel noted that cranberry should be used with caution in transplant patients due to possible drug to drug interaction with the immunosuppressive medications.

KEY FINDINGS

This evidence is based on fifty randomized controlled trials and quasi-RCTs of children and adults with recurrent UTI (n=8,857). Taking cranberries as a juice, syrup, tablets or powder reduced the number of UTIs in women with recurrent UTIs, in children with UTIs and in people susceptible to UTIs following an intervention such as bladder radiotherapy. However, UTIs did not appear to be reduced in elderly institutionalized men and women, in adults with neuromuscular bladder dysfunction and incomplete bladder emptying or in pregnant women. Abdominal pain was the most common side effect noted in a few numbers of subjects.

Certainty of evidence was low due to inconsistency, imprecision, and increased risk of bias.

INTRODUCTION

Recurrent urinary tract infection (rUTI) is defined as at least 3 episodes of a UTI in 12 months, or at least two episodes in 6 months. It is more common in women with a lifetime incidence of 50-60%.[1] Recurrent UTI have a high impact on public health due to its high direct and indirect costs. Cranberries contain proanthocyanidins (PAC), which inhibit the adherence of p-fimbriated Escherichia coli to the urothelial cells lining the bladder. Cranberry products have been used for several decades to prevent urinary tract infections [2] as an alternative to antibiotic prophylaxis because of its adverse effects and development of antibiotic-resistant bacteria.[3]

REVIEW METHODS

A systematic search was done from the last published clinical practice guideline in 2015 until April 30, 2023, using Medline, CENTRAL, and Google Scholar with a

combined MeSH and free text search using the terms cranberry, Vaccinium macrocarpon, prevention, prophylaxis, recurrent urinary tract infection. Ongoing studies were explored through the NIH clinicaltrials.gov and other trial registries. Preprints were also searched using medRxiv/bioRxiv. Only randomized controlled trials and systematic reviews and meta-analyses in English on cranberry in recurrent UTI were included. One systematic review and meta-analysis on cranberries for preventing urinary tract infections done by Williams, et al from The Cochrane database of systematic reviews published in April 2023 was found.[4] By using AMSTAR 2, Cranberries for preventing urinary tract infections (Review) by Williams G, et.al is a high-quality review.

RESULTS

Characteristics of included studies

Fifty randomized controlled trials and quasi-RCTs are included (six cross-over studies; 34 parallel group studies with two arms; eight studies with three arms and two studies with four arms and a factorial design) with a total of 8,857 randomized participants.

Types of participants included in the studies were the following:

1. Women with a history of recurrent urinary tract infections (16 RCTs) [7,8,11,14,26,27,30,32,36,40,43,44,45,46,49,51]
2. Elderly institutionalized men and women (7 RCTs) [6,9,12,22,24,25,32]
3. Pregnant women (3 RCTs) [16,53,54]
4. Children at risk of repeat UTIs (8 RCTs) [5,15,18,37,48,52,19,38]
5. Adults with neuromuscular dysfunction of the bladder and incomplete bladder emptying (9 RCTs) [21,23,28,29,31,39,41,42,50]
6. Adults with susceptibility to urinary tract infection associated with an intervention (7 RCTs) [10,12,17,20,34,35,47]

Cranberry forms included were the following:

1. Cranberry juice or juice concentrate (19 RCTs, n= 3,936) [5,6,8,13,16,18,19,22,26,30,32,37,38,43,45,46,48,52,53]
2. Cranberry tablets, capsules, or powder (29 RCTs, n = 4,682) [7,9,10,11,12,14,15,17,20,21,23,24,25,28,29,31,33,34,35,36,39,40,41,42,47,49,50,51,54]
3. Compared cranberry juice and tablets with placebo (1 RCT, n= 148) [44]
4. Compared cranberry tablets plus a probiotic with placebo (1 RCT, n=89) [27]

EFFICACY MAIN OUTCOMES:

1. Symptomatic, culture-verified UTIs. Symptomatic UTIs were defined as having one or more symptoms of dysuria, frequency, urgency, and/or fever.
2. The number of participants with symptoms of UTIs without culture verification
3. The number of participants with culture-verified UTIs without symptoms

1.Symptomatic, culture-verified urinary tract infection

Based on 26 studies (n=6,211), cranberry products reduced the risk of symptomatic, culture-verified UTIs in all patient groups regardless of dosage form with RR = 0.70 (95% CI 0.58 to 0.84; I^2=69%). Benefit was observed among women and children with recurrent UTI and adults who are UTI susceptible due to an intervention. See Appendix 9: Appendix Figure 9.9.1.

Cranberry products reduce the risk of symptomatic culture-verified UTIs in women with recurrent UTIs based on 8 studies {[40,26,49,44,8,43,30,46] (n=1,555)} with RR=0.74 (95% CI 0.55 to 0.99; I^2=54%). Cranberry products reduced the risk of subsequent symptomatic UTIs in children at risk of UTI on 5 studies {[5,18,52,15,37] (n = 504)} with RR= 0.46, (95% CI 0.32 to 0.68; I^2=21%). Cranberry products reduced the risk of UTIs in participants undergoing an intervention on 6 studies {[34,47,17,35,20,10] (n=1,434 participants)] with RR= 0.47 (95% CI 0.37 to 0.61; I^2 = 0%); low certainty evidence. See Appendix 9: Appendix Figure 9.9.1.

However, cranberry products may provide little or no benefit in institutionalized elderly in residential care in 3 RCTs {[32,25,12] (n=1,489)} with RR = 0.93 (95% CI 0.67 to 1.30; I^2=12.9%), pregnant women in 3 studies {[54,53,16] (n= 765 participants)} with RR =1.06 (95% CI 0.75 to 1.50; I^2=3%) and those with bladder emptying issues in 3 studies {[50,21,41] (n=464 participants)} with RR=0.97 (95% CI 0.78 to 1.19; I^2=0%). See Appendix 9: Appendix Figure 9.9.1.

2. The number of participants with symptoms of UTIs without culture verification
Cranberry may reduce clinical UTIs on 6 studies (n=2001)} with RR=0.73 (95% CI 0.58 to 0.90; I^2 = 45%). These were based on two studies of women with recurrent UTIs (n=518: RR 0.69, 95% CI 0.51 to 0.94; I^2 = 39%) [7,30], two studies of elderly institutionalized men and women (n=1113: RR 0.91, 95% CI 0.77 to 1.08; I^2 = 0%) [12,25], and two studies of people with a susceptibility to UTIs due to an intervention (n=370: RR 0.55, 95% CI 0.36 to 0.82; I^2 = 0%) [20,35]. Thus, there is benefit of cranberry in these different patient groups.

3. The number of participants with culture-verified UTIs without symptoms
Cranberry may be of no benefit in preventing positive urine cultures on 3 studies (n=344) with RR=0.92 (95% CI 0.71 to 1.21; I^2 = 0%). Two studies (N=209) were in the elderly [6,24] and one study (n=135) studied adults with bladder emptying issues related to multiple sclerosis [31].

EFFICACY OTHER OUTCOMES:

Death
Four studies [11,12,25,32] reported the number of deaths occurring in each arm of the study. Cranberry products may make no difference to the risk of death (n=1574 participants) with RR=1.07 (95% CI 0.89 to 1.28; I^2 = 0%). (Appendix 9: Appendix Figure 9.9.2)

Gastrointestinal adverse events
Ten studies [7,10,21,27,32,35,40,42,44,54] reported GI adverse events Cranberry products probably make no difference to the risk of GI adverse events (n=2166 participants) with RR=1.33 (95% CI 1.00 to 1.77; I^2 = 0%; moderate certainty evidence). (A Appendix 9: Appendix Figure 9.9.3)

Subgroups
Form*:* Cranberry tablets or powder and Cranberry juice or syrup versus placebo or no treatment
Outcome: Symptomatic, culture-verified urinary tract infection

Overall, cranberry tablets or powder and Cranberry juice or syrup compared to placebo, or no treatment may reduce the risk of symptomatic, culture-verified UTIs. For cranberry tablets or powder, there were 16 studies with 3,473 participants.[40,44,49,25,12,54,15,50,21,41,34,47,17,35,20,10] Efficacy for cranberry tablet or powder is RR=0.65 (95% CI 0.49 to 0.84; I^2 = 64%). For cranberry juice or syrup, there were 13 studies with 2831 participants.[26,44,8,43,43,30,46,5,18,52,37,32,53,16] Efficacy for cranberry juice or syrup is RR=0.78 (95% CI 0.62 to 0.97; I^2 = 57%).

CERTAINTY OF EVIDENCE

Study design in approximately half of the studies was relatively robust and free from significant bias. Selection bias was a concern in many studies as it was unclear how and why people were identified for admission to the study. Many studies failed to report adherence numbers including some of the studies that reported a method for measuring adherence.

The certainty of the evidence was low for all the five main outcomes (symptomatic culture verified UTI, symptomatic UTI without culture and asymptomatic but culture verified UTI, death, and GI adverse events). Overall certainty of evidence was downgraded to low due to inconsistency (moderate heterogeneity), imprecision (wide confidence intervals) and moderate risk of bias due to lack of reporting of randomization methodology, concealment, and blinding. (Table 9.1A and Appendix 8: Appendix Table 8.9A)

For specific populations it was moderate for the analyses of women with recurrent UTIs and for children. The certainty of evidence was low for pregnant, for people with a susceptibility to UTIs due to an intervention, for elderly men and women and for adults with bladder emptying issues because of imprecision and heterogeneity between studies (Table 9.1B). There were too few studies to assess the certainty of the evidence in studies satisfactorily in studies comparing cranberry to other interventions such as probiotics or antibiotics. (Table 9.1B and Appendix 8: Appendix Table 8.9B)

Table 9.1A. Summary of findings (any cranberry product versus placebo or control for preventing urinary tract infection)

Critical OUTCOMES	BASIS (Total Participants/ Number of Studies)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Symptomatic, culture-verified urinary tract infection	6,211 (26 RCTs)	RR 0.70	0.58 - 0.84	Beneficial	Low
With symptoms of UTI, without culture verification	2,001 (6 RCTs)	RR 0.73	0.58 - 0.90	Beneficial	Low
With culture-verified UTI, without symptoms	344 (3 RCTs)	RR 0.92	0.71 - 1.21	Inconclusive	Low
Death	1,574 (4 RCTs)	RR 1.07	0.89 - 1.28	Inconclusive	Low

Gastrointestinal adverse events	2,166 (10 RCTs)	RR 1.33	1.00 -1.77	Inconclusive	Low

Table 9.1B. Summary of findings on outcome (any cranberry product versus placebo or control for preventing urinary trac infection)

Critical OUTCOMES for Symptomatic, culture-verified UTI	BASIS (Total Participants/ Number 0f Studies)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Symptomatic, culture-verified urinary tract infection	**6211 (26)**	**0.70**	**0.58 - 0.84**	**Beneficial**	**Low**
Women with recurrent UTI	1,555 (8)	RR 0.74	0.55 -0.99	Beneficial	Moderate
Elderly men and women in institutions	1,489 (3)	RR 0.93	0.67 -1.30	Equivalent	Low
Pregnant	765 (3)	RR 1.06	0.75 -1.50	Equivalent	Low
Children	504 (5)	RR 0.46	0.32 -0.68	Beneficial	Moderate
Adults with bladder emptying issues or multiple sclerosis	464 (3)	RR 0.97	0.78 -1.19	Equivalent	Low
People with a susceptibility to a UTI due to an intervention	1,434 (6)	RR 0.47	0.37 -0.61	Beneficial	Low
Death	1,574 (4)	RR 1.07	0.89-1.28	Equivalent	Moderate
Gastrointestinal adverse events	2,166 (10)	RR 1.33	1.00 -1.77	Equivalent	Moderate

RECOMMENDATIONS FROM OTHER GROUPS

Table 9.2. Summary of recommendations from other groups and agencies.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
National Institute for Health and Care Excellence (NICE) [55]	The committee recognized that cranberry products are used widely and discussed the very low-quality evidence showing some benefit for reducing the risk of UTIs, specifically in non-pregnant women, and children and young people. They were also aware that there was no evidence to suggest benefit in older women. The committee also noted the conflicting evidence for cranberry products in reducing the risk of antimicrobial resistance. Taking account of the limitations of the evidence, and the need to minimize antimicrobial resistance, the committee agreed that some women who are not pregnant and some children and young people under 16 may wish to try cranberry products as a self-care treatment. However, due to safety concerns with delayed treatment, particularly in children and young people, the committee agreed that cranberry products should	Conditional recommendation, very low-quality evidence

	only be considered in this population following advice from a pediatric specialist. The committee recognized that there was some evidence to suggest that cranberry juice was not significantly better than placebo in non-pregnant women, while cranberry capsules showed a significant benefit. However, due to significant limitations in the evidence the committee was not able to recommend a specific cranberry product. The committee discussed the sugar content of cranberry products, and based on their experience, agreed that people should be advised to take account of their daily sugar intake if using cranberry products.	
Philippine Clinical Practice Guidelines on UTI 2015 Update: Part 2 [56]	Cranberry products are not recommended for the prevention of urinary tract infections in populations at risk because there is no consistent evidence as to Recurrent UTI in women	Conditional recommendation, moderate quality of evidence

ONGOING STUDIES AND RESEARCH GAPS

There are 7 on-going randomized controlled trials found listed in clinical trials.gov on the use of cranberry for UTI (Table 9.3).

Table 9.3. Characteristics of ongoing studies.

Clinical Trial Identifier/Title	Population	Intervention	Comparator	Outcome
ACTRN12605000626662 Cranberry capsules for the prevention of urinary tract infection in an elderly population Start date 1/11/2005	Elderly people Australia	Cranberry tablets	placebo	incidence of UTI in elderly client
Amador-Mulero 2014 Effectiveness of red cranberries ingestion on urinary tract infections in pregnant women	Healthy first-time mothers belonging to these healthcare centers	1 capsule daily cranberry extract (118 mg PAC)		Incidence of UTI
ISRCTN55813586 Clinical dosage and effectiveness study of ShanStar® cranberry supplement for prevention and intervention against women's urinary tract infections Start date 31/01/2011 to 30/04/2011	Women	ShanStar® cranberry extract 150 mg and 300 mg/day		Effectiveness of ShanStar® cranberry extract against recurrent UTIs on the basis of symptoms, bacteriuria and pyuria in the urine and urine culture
NCT00100061 Dose response to cranberry of women with recurrent UTIs Start date May 2007	Women with recurrent UTI	Cranberry juice		UTI
NCT03597152 Nutritional supplementation for recurrent urinary tract infections in women Start date 1-8-2020;	250 women, aged 18 to 75 years, who have suffered from 3 to 4 uncomplicated UTI in the	Dietary supplement: WelTract (contains extracts from hibiscus flowers and	placebo	The primary outcome will be time to recurrence of next UTI

	past 12 months	cranberry fruit, lactoferrin, D-mannose, and vitamins C and D)		
Cranberry for the prevention of urinary tract infections Start date 1 September 2022	Diabetic women ≥ 70 years	Anthocran phytosome	placebo	Urinalysis, urine culture

To determine the dose with the highest efficacy, safety, and tolerability in patients at risk of symptomatic UTIs, further studies must be done. The amount of proanthocyanidins (PAC) within cranberry products should be standardized with labels to include its PAC content. More studies are also needed to assess the relative efficacy and safety of cranberry products compared with antibiotics or probiotics to prevent symptomatic UTIs.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

Most cranberry products marketed in the country are registered with the Philippine Durg Administration as food supplement with no approved therapeutic claims.

Table 9.4 shows the list of cranberry products which are sold in the country online or in store with the computed monthly and daily expenses based on the recommended dosage or manufacturer's recommendations.

Table 9.4. List of cranberry products sold in the country.

Drug Form	Treatment cost
Capsule Form:	Recommended for UTI prevention: capsules containing 36 mg PACs (proanthocyanidins) taken twice a day
Puritan's Pride Cranberry 25,000 mg 60 caps…… Php 929	One cap daily: Php 464.50 per month or Php 15.50/day
NOW foods Cranberry caps 1,400 mg 100 caps……...Php 1,500	2 caps daily: Php 900/month or Php 30/day
STADA Uriberry caps 5000 mg 30 tabs……Php 490	1 tab daily:Php 490/month or Php 16.50 daily
Juice Form:	Recommended for UTI prevention is daily consumption of 300 mL of cranberry juice
Ocean Spray Cranberry Juice Cocktail 3L……Php 403	300 mL daily: Php 1,200/month or Php 40 daily
Lakewood Organic Pure Cranberry Juice 946 ml……...Php 900	3-4 fluid ounces twice daily. 100 mL 2x daily: Php 6,300/month or Php 210 daily
Old Orchard Cranberry Juice cocktail 1.8 L……...Php 370	300 mL daily: Php 3,690/month or Php 123 daily

No local studies on cost effectiveness analysis have been done yet but there were three found from Netherlands and Canada. The study by Stothers [57], et al concluded that taking Cranberry has the potential to reduce doctor's visits. The study by van de Hout [58], et al, concluded that in low-risk UTI, taking cranberry is neither effective nor

cost-effective while in high-risk UTI, taking cranberry may be effective in preventing UTIs but is not likely to be cost-effective. Lastly, the study by Bosman et.al [59], which compared cranberry to TMP-SMX, showed that cranberry prophylaxis to prevent UTIs is less effective and more expensive than TMP-SMX prophylaxis. (See Table 9.5)

Table 9.5. Summary of studies with cost effectiveness analysis.

<table>
<tr><th>Study ID</th><th>Country</th><th>Cost/ Results</th><th>Cost in Php</th></tr>
<tr><td>PATTERNS AND COSTS OF HEALTH CARE UTILIZATION PRIOR, DURING AND FOLLOWING EXPOSURE TO CRANBERRY IN THE PREVENTION OF FEMALE URINARY TRACT INFECTION: RESULTS FROM A RANDOMIZED CONTROLLED CLINICAL TRIAL (RCT) INVOLVING WOMEN WITH RECURRENT UTI.
Stothers,et al

THE JOURNAL OF UROLOGYVol. 199, No. 4S, Supplement, Monday, May 21, 2018</td><td>Vancouver, Canada</td><td>All costs include urinalysis (U/A) within 7 days and number of visits associated with UTI.
<table>
<tr><th>CRANBERRY</th><th>Average/year UTI visits before Intervention</th><th>Average/year UTI visits after Intervention</th></tr>
<tr><td>Placebo</td><td>2.8 visits</td><td>?</td></tr>
<tr><td>Low Dose</td><td>2.8 visits</td><td>1 visit</td></tr>
<tr><td>Medium Dose</td><td>2.6 visits</td><td>?</td></tr>
</table>
CONCLUSIONS: Exposure to low and medium doses of cranberry juice for one year has the potential to reduce specialist and GP visits and associated costs among women with a history of recurrent UTI.</td><td></td></tr>
<tr><td>Cost-Effectiveness of Cranberry Capsules to Prevent Urinary Tract Infection in Long-Term Care Facilities: Economic Evaluation with a Randomized Controlled Trial van den Hout, et al
J Am Geriatr Soc 62:111–116, 2014.</td><td>Netherlands</td><td>CONCLUSION: In high-UTI-risk residents, taking cranberry capsules may be effective in preventing UTIs but is not likely to be cost-effective in the investigated dosage, frequency, and setting.
increased lifelong total costs by €941 (95% CI = €779–1,055)

In low-UTI-risk LTCF residents, taking cranberry capsules twice daily is neither effective nor cost-effective.
Estimated lifelong costs of €1,012 for cranberry use</td><td>Php 55,000 (Php 46.000-Php 62.000)

Php 60,000</td></tr>
<tr><td>Cost-Effectiveness of Cranberries vs Antibiotics to Prevent Urinary Tract Infections in Premenopausal Women: A Randomized Clinical Trial
Bosmans, et al

PLoS One. 2014 Apr 4;9(4):e91939. doi: 10.1371</td><td>Netherlands</td><td>Results: Cranberry prophylaxis was less effective than TMP-SMX prophylaxis, but the differences in clinical outcomes were not statistically significant.

Costs after 12 months in the cranberry group were statistically significantly higher than in the TMP-SMX group (mean difference €249, 95% confidence interval 70 to 516).
Cost-effectiveness planes and costeffectiveness acceptability curves showed that cranberry prophylaxis to prevent UTIs is less effective and more expensive than (dominated by) TMP-SMX prophylaxis.

Conclusion: In premenopausal women with recurrent UTIs, cranberry prophylaxis is not cost-effective compared to TMPSMX prophylaxis.</td><td>Php 14,000 (Php 4,000-Php 30,000)</td></tr>
</table>

Patient's values and preference, equity, acceptability, and feasibility

The challenge of long-term antibiotic use and the corresponding risk for antibiotic resistance and medical costs of recurrent urinary tract infection has paved way for search for alternatives such as cranberry use.[60] Cranberry being a natural product and non-prescription supplement is accessible locally and would not induce antimicrobial resistance.

Four trials showed cranberry patient withdrawals were as high as > 40%.[61] Taste is one of the factors affecting patient adherence.[19]

Another possible factor to affect patient acceptability is the earlier review in 2012 which reported cranberry side effects including reflux, mild nausea, frequent bowel movements, headaches, elevation in blood glucose levels and a cutaneous reaction;[62] but these are not significant in our current review of literature.

Drug interactions among patients with other co-morbidities and maintenance medications will also be considered as cranberries may have in its contents, CYP enzyme-inhibiting flavonoids which may interact with medications such as warfarin.[63] The National Center for Complementary and Integrative Health (NCCIH) has also advised the use of cranberry in individuals at risk of urolithiasis, but this was based in one small study (n=5) with the premise that cranberry tablet preparations contain vitamin C, which has been independently shown to increase urinary oxalate excretion.[64]

REFERENCES

1. Medina, Martha, and Edgardo Castillo-Pino. "An introduction to the epidemiology and burden of urinary tract infections." Therapeutic advances in urology vol. 11 1756287219832172. 2 May. 2019, doi:10.1177/1756287219832172
2. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2012 Oct 17;10(10):CD001321. doi: 10.1002/14651858.CD001321.pub5. Update in: Cochrane Database Syst Rev. 2023 Apr 17;4:CD001321. PMID: 23076891; PMCID: PMC7027998.
3. Beerepoot MAJ, ter Riet G, Nys S, et al. Cranberries vs Antibiotics to Prevent Urinary Tract Infections: A Randomized Double-blind Noninferiority Trial in Premenopausal Women. Arch Intern Med. 2011;171(14):1270–1278. doi:10.1001/archinternmed.2011.306
4. Williams G, Hahn D, Stephens JH, Craig JC, Hodson EM. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub6.
5. Afshar K, Stothers L, Scott H, MacNeily AE. Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. Journal of Urology 2012;188(4 Suppl):1584-7. [MEDLINE: 22910239]
6. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 1994;271(10):751-4. [MEDLINE: 8093138]
7. Babar A, Moore L, Leblanc V, Dudonne S, Desjardins Y, Lemieux S, et al. High dose versus low dose standardized cranberry proanthocyanidin extract for the prevention of recurrent urinary tract infection in healthy women: a double blind randomized controlled trial. BMC Urology 2021;21(1):44. [MEDLINE: 33757474]
8. Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clinical Infectious Diseases 2011;52(1):23-30. [MEDLINE: 21148516]
9. Bianco L, Perrelli E, Towle V, Van Ness PH, Juthani-Mehta M. Pilot randomized controlled dosing study of cranberry capsules for reduction of bacteriuria plus pyuria in female nursing home residents. Journal of the American Geriatrics Society 2012;60(6):1180-1. [MEDLINE: 22690994]
10. Bonetta A, Roviello G, Generali D, Zanotti L, Cappelletti MR, Pacifico C, et al. Enteric-coated and highly standardized cranberry extract reduces antibiotic and nonsteroidal anti inflammatory drug

use for urinary tract infections during radiotherapy for prostate carcinoma. Research & Reports in Urology 2017;9:65-9. [MEDLINE: 28491861]
11. Bruyere F, Azzouzi AR, Lavigne JP, Droupy S, Coloby P, Game X, et al. A multicenter, randomized, placebo-controlled study evaluating the efficacy of a combination of propolis and cranberry (Vaccinium macrocarpon) (DUAB®) in preventing low urinary tract infection recurrence in women complaining of recurrent cystitis. Urologia Internationalis 2019;103(1):41-8. [MEDLINE: 31117097]
12. Caljouw MA, van den Hout WB, Putter H, Achterberg WP, Cools HJ, Gussekloo J. Effectiveness of cranberry capsules to prevent urinary tract infections in vulnerable older persons: a double-blind randomized placebo-controlled trial in long term care facilities. Journal of the American Geriatrics Society 2014;62(1):103-10. [MEDLINE: 25180378]
13. Cowan CC, Hutchison C, Cole T, Barry SJ, Paul J, Reed NS, et al. A randomised double-blind placebo controlled trial to determine the effect of cranberry juice on decreasing the incidence of urinary symptoms and urinary tract infections in patients undergoing radiotherapy for cancer of the bladder or cervix. Clinical Oncology 2012;24(2):e31-8. [MEDLINE: 21703829]
14. De Leo V, Cappelli V, Massaro MG, Tosti C, Morgante G. Evaluation of the effects of a natural dietary supplement with cranberry, Noxamicina® and D-mannose in recurrent urinary infections in perimenopausal women. Minerva Ginecologica 2017;69(4):336-41. [MEDLINE: 28608666]
15. Dotis J, Printza N, Stabouli S, Pavlaki A, Samara S, Papachristou F. Efficacy of cranberry capsules to prevent recurences of urinary tract infections [abstract no: P351]. Pediatric Nephrology 2014;29(9):1793-4. [EMBASE: 71662748]
16. Essadi F, Elmehashi MO. Efficacy of cranberry juice for the prevention of urinary tract infections in pregnancy [abstract no: PS 310]. Journal of Maternal-Fetal & Neonatal Medicine 2010;23(Suppl 1):378. [EMBASE: 70200859]
17. Fernandes A, Pereira T, Mendes A, Birne R, Matias P, Jorge C, et al. Are cranberry capsules effective in preventing urinary tract infections in kidney transplant women?-Randomized trial [abstract no: MP716]. Nephrology Dialysis Transplantation 2016;31(Suppl 1):i577. [EMBASE: 72327567]
18. Ferrara P, Romaniello L, Vitelli O, Gatto A, Serva M, Cataldi L. Cranberry juice for the prevention of recurrent urinary tract infections: a randomized controlled trial in children. Scandinavian Journal of Urology & Nephrology 2009;43(5):369-72. [MEDLINE: 19921981]
19. Foda MM, Middlebrook PF, Gatfield CT, Potvin G, Wells G, Schillinger JF. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. Canadian Journal of Urology 1995;2(1):98-102. [MEDLINE: 12803726]
20. Foxman B, Cronenwett AE, Spino C, Berger MB, Morgan DM. Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. American Journal of Obstetrics & Gynecology 2015;213(2):194-8. [MEDLINE: 25882919]
21. Gallien P, Amarenco G, Benoit N, Bonniaud V, Donze C, Kerdraon J, et al. Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: a multicenter, randomized, placebo-controlled, double-blind trial. Multiple Sclerosis 2014;20(9):1252-9. [MEDLINE: 24402038]
22. Haverkorn MJ, Mandigers J. Reduction of bacteriuria and pyuria using cranberry juice. JAMA 1994;272(8):590. [MEDLINE: 8057506]
23. Hess MJ, Hess, PR, Sullivan MR, Nee M, Yalla SV. Evaluation of cranberry tablets for the prevention of urinary tract infections in spinal cord injured patients with neurogenic bladder. Spinal Cord 2008;46(9):622-6. [MEDLINE: 18392039]
24. Juthani-Mehta M, Perley L, Chen S, Dziura J, Gupta K. Feasibility of cranberry capsule administration and clean-catch urine collection in long-term care residents. Journal of the American Geriatrics Society 2010;58(10):2028-30. [MEDLINE: 20929476]
25. Juthani-Mehta M, Van Ness PH, Bianco L, Rink A, Rubeck S, Ginter S, et al. ENect of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: a randomized clinical trial. JAMA 2016;316(18):1879-87. [MEDLINE: 27787564]
26. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. BMJ 2001;322(7302):1571-3. [MEDLINE: 11431298]
27. Koradia P, Kapadia S, Trivedi Y, Chanchu G, Harper A. Probiotic and cranberry supplementation for preventing recurrent uncomplicated urinary tract infections in premenopausal women: a controlled pilot study. Expert Review of Anti infective Therapy 2019;17(9):733-40. [MEDLINE: 31516055
28. Linsenmeyer TA, Harrison B, Oakley A, Kirshblum S, Stock JA, Millis SR. Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders

secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study. Journal of Spinal Cord Medicine 2004;27(1):29-34. [MEDLINE: 15156934]
29. Lopes De Carvalho L, Francavilla G, Motta R, Brichetto G. Dmannose, cranberry and vitamin C are effective in preventing urinary tract infections in multiple sclerosis subjects [abstract no: 108]. Multiple Sclerosis 2012;18(5):S12-3. [EMBASE: 70762266]
30. Maki KC, Kaspar KL, Khoo C, Derrig LH, Schild AL, Gupta K. Consumption of a cranberry juice beverage lowered the number of clinical urinary tract infection episodes in women with a recent history of urinary tract infection [Erratum in: Am J Clin Nutr. 2017 Aug;106(2):708]. American Journal of Clinical Nutrition 2016;103(6):1434-42. [MEDLINE: 27251185]
31. McGuiness SD, Krone R, Metz LM. A double-blind, randomized, placebo-controlled trial of cranberry supplements in multiple sclerosis. Journal of Neuroscience Nursing 2002;34(1):4-7. [CENTRAL: CN-00724988]
32. McMurdo ME, Bissett LY, Price RJ, Phillips G, Crombie IK. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo controlled trial. Age & Ageing 2005;34(3):256-61. [MEDLINE: 15863410]
33. McMurdo ME, Argo I, Phillips G, Daly F, Davey P. Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. Journal of Antimicrobial Chemotherapy 2009;63(2):389-95. [MEDLINE: 19042940]
34. Mohammed MB, Razzaq BA, Al-Naqqash MA, Jasim SY. ENects of cranberry-PACs against urinary problems associated with radiotherapy in Iraqi patients with bladder carcinoma. International Journal of Pharmaceutical Sciences Review & Research 2016;39(2):179-88. [EMBASE: 611820126]
35. Mooren ES, Liefers WJ, de Leeuw JW. Cranberries after pelvic floor surgery for urinary tract infection prophylaxis: A randomized controlled trial. Neurourology & Urodynamics 2020;39(5):1543-9. [MEDLINE: 32449530
36. NAPRUTI 2011. Beerepoot MA, Stobberingh EE, Geerlings SE. Beerepoot MA, ter Riet G, Nys S, van der Wal WM, de Borgie CA, de Reijke TM, et al. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind non inferiority trial in premenopausal women. Archives of Internal Medicine 2011;171(14):1270-8. [MEDLINE: 21788542]
37. Salo J, Kontiokari T, Helminen M, Korppi M, Nieminen T, Pokka T, et al. Randomized trial of cranberry juice for the prevention of recurrences of urinary tract infections in children [abstract no: P1356]. Clinical Microbiology & Infection 2010;16(Suppl 2):S385-6. [EMBASE: 70195963]
38. Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. Journal of Pediatrics 1999;135(6):698-702. [MEDLINE: 10586171]
39. Scovell J, Fletcher S, Stewart J, Khavari R. A prospective randomized double-blinded placebo control trial on the effects of cranberry supplementation on bacterial colonization and symptomatic urinary tract infections in females with neurogenic bladder dysfunction dependent on self catheterization [abstract no: PD8-07]. Journal of Urology 2015;193(4 Suppl 1):e192-3. [EMBASE: 71858240]
40. Sengupta K, Alluri KV, Golakoti T, Gottumukkala GV, Raavi J, Kotchrlakota L, et al. A randomized, double blind, controlled, dose dependent clinical trial to evaluate the efficacy of a proanthocyanidin standardized whole cranberry (Vaccinium macrocarpon) powder on infections of the urinary tract. Current Bioactive Compounds 2011;7(1):39-46. [EMBASE: 361592064]
41. SINBA 2007. Lee BB, Haran MJ, Hunt LM, Simpson JM, Marial O, Rutkowski SB, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. Spinal Cord 2007;45(8):542-50. [MEDLINE: 17043681]
42. Singh I, Gautam LK, Kaur IR. Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic E. coli: a randomized placebo-controlled clinical research study. International Urology & Nephrology 2016;48(9):1379-86. [MEDLINE: 27314247]
43. Stapleton AE, Dziura J, Hooton TM, Cox ME, Yarova-Yarovaya Y, Chen S, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clinic Proceedings 2012;87(2):143-50. [MEDLINE: 22305026]
44. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Canadian Journal of Urology 2002;9(3):1558-62. [MEDLINE: 12121581]
45. Stothers L, Brown P, Levine M, Fenster H, Berkowitz J. A randomized controlled trial examining dose response of cranberry in the treatment of lower urinary tract infections in women and human

urine cranberry metabolites [abstract]. Canadian Urological Association Journal 2016;10(5-6 Suppl 1):S11. [EMBASE: 617745754]
46. Takahashi S, Hamasuna R, Yasuda M, Arakawa S, Tanaka K, Ishikawa K, et al. A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. Journal of Infection & Chemotherapy 2013;19(1):112-7. [MEDLINE: 22961092]
47. Temiz Z, Cavdar I. The effects of training and the use of cranberry capsule in preventing urinary tract infections after urostomy. Complementary Therapies in Clinical Practice 2018;31:111-7. [MEDLINE: 29705442]
48. Uberos J, Nogueras-Ocana M, Fernandez-Puentes V, Rodriguez Belmonte R, Narbona-López E, Molina-Carballo A, et al. Cranberry syrup vs trimethoprim in the prophylaxis of recurrent urinary tract infections among children: a controlled trial. Open Access Journal of Clinical Trials 2012;4:31–8. [EMBASE: 2012351759]
49. Vostalova J, Vidlar A, Simanek V, Galandakova A, Kosina P, Vacek J, et al. Are high proanthocyanidins key to cranberry eNicacy in the prevention of recurrent urinary tract infection? Phytotherapy Research 2015;29(10):1559-67. [MEDLINE: 26268913]
50. Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. Journal of Spinal Cord Medicine 2004;27(1):35-40. [MEDLINE: 15156935]
51. Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA Jr. Cranberry concentrate: UTI prophylaxis. Journal of Family Practice 1997;45(2):167-8. [MEDLINE: 9267377]
52. Wan KS, Liu CK, Lee WK, Ko MC, Huang CS. Cranberries for preventing recurrent urinary tract infections in uncircumcised boys. Alternative Therapies in Health & Medicine 2016;22(6):20-3. [MEDLINE: 27866177]
53. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. Journal of Urology 2008;180(4):1367-72. [MEDLINE: 18707726]
54. Wing DA, Rumney PPJ, Hindra S, Le J, Nageotte M. Evaluation of compliance and tolerability of cranberry capsules in pregnancy for the prevention of asymptomatic bacteriuria in pregnancy [abstract no: T-119]. Reproductive Sciences 2015;22(Suppl 1):146A. [EMBASE: 71847498]
55. Urinary tract infection (recurrent): antimicrobial prescribing NICE guideline [NG112] Published: 31 October 2018
56. CPG for UTI in Adults 2015 Update: Part 2 https://www.psmid.org/diagnosis-and-management-of-urinary-tract-infections-in-adults-2015-update- part-2/
57. Stothers L,Levine M,Berkowitz J, Brown P, Patterns and Costs of Health Care Utilization prior,during and following exposure to a Cranberry in the Prevention of female Urinary Tract Infection: Results from a Randomized Controlled Clinical Trial (RCT) involving women with recurrent UTI. THE JOURNAL OF UROLOGY Vol. 199, No. 4S, Supplement, Monday, May 21, 2018
58. van den Hout WB, Caljouw MA, Putter H, Cools HJ, Gussekloo J. Cost-effectiveness of cranberry capsules to prevent urinary tract infection in long-term care facilities: economic evaluation with a randomized controlled trial. J Am Geriatr Soc. 2014 Jan;62(1):111-6. doi: 10.1111/jgs.12595. PMID: 25180379; PMCID: PMC4233962.
59. Bosmans JE, Beerepoot MA, Prins JM, ter Riet G, Geerlings SE. Cost-effectiveness of cranberries vs antibiotics to prevent urinary tract infections in premenopausal women: a randomized clinical trial. PLoS One. 2014 Apr 4;9(4):e91939. doi: 10.1371/journal.pone.0091939. PMID: 24705418; PMCID: PMC3976255.
60. Stapleton, Ann. “Novel approaches to prevention of urinary tract infections.” Infectious disease clinics of North America vol. 17,2 (2003): 457-71. doi:10.1016/s0891-5520(03)00010-2
61. Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. Molecular Nutrition & Food Research. 2007 Jun;51(6):738-45. doi: 10.1002/mnfr.200600275
62. Hisano M, Bruschini H, Nicodemo AC, Srougi M. Cranberries and lower urinary tract infection prevention. Clinics (Sao Paulo). 2012;67(6):661-8. doi: 10.6061/clinics/2012(06)18. PMID: 22760907; PMCID: PMC3370320.
63. Pham, David Q, and Antony Q Pham. “Interaction potential between cranberry juice and warfarin.” American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists vol. 64,5 (2007): 490-4. doi:10.2146/ajhp060370
64. Redmond, Elaine J et al. “The influence of dietary supplementation with cranberry tablets on the urinary risk factors for nephrolithiasis.” World journal of urology vol. 37,3 (2019): 561-566. doi:10.1007/s00345-018-2344-1

Question 10. Among patients with recurrent UTI, what are the indications (i.e., predisposing conditions, risk factors) for referral to a specialist?

Recommendations

Among children and adults with recurrent UTI, we **recommend** referral to a higher level of care. ***(Best practice statement)***

Consensus Issues

- The panel recommended referral to a higher level of care as to not delay treatment and facilitate identification of an anatomic or functional cause of the recurrent UTI that will require specialist care.
- The panel recognized the potential resource requirement of referral to a higher level of care. In the light of the importance of such escalation to decrease the risk of delated treatment of conditions requiring specialist care, the panel recommends that processes and policies be put in place to allow easy access to specialty care across the country.

KEY FINDINGS

The review found six observational studies that evaluated risk factors for recurrent UTI (rUTI) among adult females, which comprise the indications for referral of patients with rUTI to a higher level of care.

Post-void residual urine greater than 30 ml, prolapse or cystocoele, previous urogynecologic surgery and age ≤ 15 years old on the 1st episode of UTI were found to significantly increase the odds of rUTI among adult females, while results for urinary incontinence were conflicting. These conditions warrant a referral to a higher level of care.

Although other factors were found to be associated with rUTI, such as nulliparity, age, history of UTI, diabetes mellitus, being sexually active, having a new sex partner and spermicide use, these were deemed not to merit specialized care, as with age, for which results were conflicting and condom use which was found not to be associated with rUTI.

All studies had high risk of bias due to selection, misclassification, recall and attrition. The risk of bias contributed to further downgrading of evidence to very low certainty due to inconsistency, indirectness, and imprecision.

INTRODUCTION

Based on the 2020 Philippine Health Statistics report, urinary tract infections (UTI) remain to be the 3rd leading cause of morbidity, with a higher prevalence in women than men.[1]

A study of UTI in the primary care setting revealed that 53 % of women above the age of 55 years and 36 % of younger women had a recurrence within one year.[2] Recurrence within six months of the 1st UTI occurs in about 25% of women.[3]

Recurrent UTI (rUTI) in a healthy non-pregnant woman with no known urinary tract abnormalities is defined by 3 or more episodes of acute uncomplicated cystitis documented by urine culture during a 12-month period OR two or more episodes in a 6- month period.[4]

Recurrent urinary tract infections have also been identified to be a risk factor for complicated UTI, and/or treatment failure.[4] including multi-drug resistant UTI.[5]

Delay in diagnosis may complicate an initially simple problem and may entail a corresponding increase in costs of work-ups and treatment, as well as significant impact on the quality of life of the patient, [6,7] including negative effects on both intimate and social relationships, self-esteem, and capacity for work.[8]

Currently, there are no guidelines as to the indications for referral of adult females with rUTI to a higher level of care, either for further diagnosis and/or management. Although several review articles include lists of conditions that may warrant further investigation or referral, firm evidence for these conditions is lacking in literature. Hence, criteria for referral should be clear and based on scientific evidence to avoid automatic referral of all patients with urinary tract infection or non-referral of those who may be at higher risk for more serious infections.

REVIEW METHODS

Initially, studies comparing the outcomes among patients with rUTI referred to a specialist versus those who were not were systematically searched. A systematic and comprehensive search in Medline thru PubMed, Cochrane Library, ClinicalTrials.gov, Chinese Clinical Trial Registry, EU Clinical Trials Register, medRxiv.org, bioRxiv.org and Google scholar, with “recurrent”, “chronic”, “complicated”, “persistent” “urinary tract infection”, “pyelonephritis” “cystitis” “bacterial urinary tract infection”, “pyuria”, bacteriuria”, “urethritis”, “pus in urine”, “UTI”, “recurrence”, “persistence”, “consultation and referral”, “physician specialist” and “primary care physician” as free text and MeSH terms was done on November 28, 2022. No studies were found. (See Appendix 3: Appendix Table 3.10 for Search Strategy and Appendix 4: Appendix Figure 4.10 for PRISMA Diagram)

Next, studies on prognostic factors leading to complications among patients with rUTI were also searched. Using free text and MeSH terms for “risk factors”, “prognostic factors”, “recurrent”, “chronic”, “complicated”, “complicated urinary tract infection”, “persistent” “urinary tract infection”, “pyelonephritis” “cystitis” “bacterial urinary tract infection”, “pyuria”, bacteriuria”, “urethritis”, “pus in urine”, “UTI”, “recurrence”, “persistence” a systematic search in the databases of MEDLINE, Cochrane Library, Clinicaltrials.gov, Google Scholar and medRxiv.org bioRxiv.org, was done from March 16 to March 24, 2023. The references of identified studies were examined to find any further potential studies for inclusion. Boolean operators (AND, OR) were employed. Although the search was limited to adult female 19+ years and systematic reviews, the yield included primary studies. Again, no studies were found.

In the absence of the above studies, studies that looked at possible risk factors associated with recurrent UTI were searched. We found six observational studies. The

observational studies were appraised using Newcastle–Ottawa scale. (See Appendix 6: Appendix Table 6.10.1-3 for Summary of Risk of Bias)

For studies with available data, odds ratios and confidence intervals were computed. For studies where computation of odds ratios was not possible, reported odds ratios were presented in the narrative. Pooling of studies was done using RevMan 5.4. Studies that provided adjusted odds ratio results were pooled using the Generic Inverse Variance analysis in RevMan. No sub-group analysis was done but results of subgroup analysis by age were presented as reported in one article.

RESULTS

Characteristics of included studies

This review identified six published observational studies, one cross-sectional, two cohort, three case control studies, that evaluated the risk factors for rUTI among adult females, which in this review may be considered as indications for referral to a higher level of care. (See Appendix 5: Appendix Table 5.10 for Characteristics of Included Studies)

The articles were heterogenous in terms of population, risk factors investigated, definition of rUTI and length of follow-up.

Populations included young university women, HMO enrollees, post-menopausal women, women enlisted with general practitioners and women referred for pelvic floor dysfunction. Only one study did sub-group analysis by age.

Risk factors investigated were age, parity, age at 1st UTI, history of UTI before menopause, diabetes, sexual intercourse, and urologic factors. Excluded were genetic risk factors such as specific blood group antigens and non-secretor phenotypes, relationship factors (e.g., number of lifetime partners and length of current relationship), and behavioral risk factors. Length of follow-up ranged from 6 months to 43 months in the three cohort studies. Pathologic factors associated with recurrent UTI are presented here.

Risk factors

Post-voiding residual volume

Pooled results of two studies (n= 1,342) showed that rUTI significantly increased with post-void residual urine greater than 30 ml [AOR=8.05 (95% CI 3.95, 16.43, I^2 56%)].[9, 10] The 2 studies had substantial heterogeneity due to a difference in the cut-off volume for post-voiding residual urine as well as in the stratification of results by age in one study. (See Appendix 8: Appendix Table 8.10.1 for the GRADE Evidence Table and Appendix 9; Appendix Figure 9.10.1 for Forest Plot)

Prolapse / cystocoele

Pooling the results of two studies (n= 1,342) demonstrated a significant increase in odds of rUTI among women with prolapse or cystocoele [AOR=1.93 (95% CI 1.40, 2.66, I^2 73%)]. The studies were substantially heterogenous due to a difference in the age of the study populations – mean age =65.7 [9] versus 58 years [10]. (See Appendix

8: Appendix Table 8.10.2 for the GRADE Evidence Table and Appendix Figure 9.10.2 for Forest Plot)

Urogynecologic surgery

Pooling the results of two studies (n=1,342) showed that previous urogynecologic surgery significantly increased the odds of rUTI among adult women [AOR=2.31 (95% CI 1.04, 5.15, I^2 80%)]. The studies, however, had considerable heterogeneity, owing to the difference in age of the study populations - mean age =65.7 [9] versus 58 years [10]. (See Appendix 8: Appendix Table 8.10.3 for the GRADE Evidence Table and Appendix Figure 9.10.3 for Forest Plot)

Urinary incontinence

Two studies (n= 1,342) showed conflicting results for urinary incontinence as a risk factor for rUTI. The study by Raz, et al [9] reported a significantly increased odds of rUTI among women with urinary incontinence [AOR=5.79 (95% CI 2.05, 16.42)]. Haylen, et al [10], however, found no significant association between rUTI and urodynamic stress incontinence (p=0.639).

Age at 1st UTI

Women who were ≤ 15 years old of age on their 1st episode of UTI, had a 4-fold increase in odds of rUTI [AOR=3.9 (95% CI 1.90, 8.00)] (n=482).[11] This factor may suggest the presence of a congenital anomaly.

Evidence for the following factors were investigated but were not considered as indications for referral to a higher level of care as they did not seem to be conditions that a primary care physician could not address, nor did they suggest conditions that reflected more complex types of urological disorders:

Demographic factors

Demographic and clinical factors found to be associated with rUTI were nulliparity in women ≤50 years old [10], history of UTI before menopause [9] and diabetes mellitus [12]. Results for age were conflicting.[10] (See Appendix 5 for GRADE Evidence Tables)

Factors related to sexual intercourse, being sexually active [13], having a new sex partner [11,14], spermicide use [11,14] and frequent vaginal intercourse [11,14], were found to be associated with rUTI, while with condom use [14] was found not to be significantly associated with rUTI. (See Appendix 8: Appendix Table 8.10.4-6 for GRADE Evidence Tables and Appendix 9: Appendix Figure.8.10.4-6 for Forest Plots)

GRADE summary of findings table

Table 10.1. GRADE Summary findings.

Outcome: Recurrent UTI					
Risk Factors	**Basis**	**Effect Size**	**95% CI**	**Interpretation**	**Certainty of Evidence**
Post-voiding residual volume >30 ml	1 case control[a] (n=202) 1 cross-sectional[b] (n=1,140)	AOR = 8.05	3.95, 16.43	Significant Risk	Very low
Prolapse/ cystocoele	1 case control (n=202) 1 cross-sectional (n=1,140)	AOR = 1.93	1.40, 2.66	Significant Risk	Very low
Urogynecologic surgery	1 case control (n=202) 1 cross-sectional (n=1,140)	AOR = 2.31	1.04, 5.15	Significant Risk	Very low
Urinary incontinence	1 case control (n=202) 1 cross-sectional (n=1,140)	AOR = 5.79 No raw data	2.05, 16.42 p = 0.639	Significant Risk No significant risk	Very low
Age at 1st UTI	1 case control (n=482)	AOR= 3.90	1.9, 8.0	Significant Risk	Very low

CERTAINTY OF EVIDENCE

All studies had high risk of bias due to selection, misclassification, recall and attrition. (See Appendix 6: Appendix Table 6.10.1-3 for Summary of Risk of Bias). The risk of bias contributed to further downgrading of evidence to very low certainty due to inconsistency and imprecision. (See Appendix 8: Appendix Table 8.10.1-12 for the GRADE Evidence Profile).

RECOMMENDATIONS FROM OTHER GROUPS

Table 10.2 Recommendations from other groups and agencies.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
NICE [NG112] Published 31 Oct 2018 [14]	Recommends referral to specialist for further investigation and management: • Men aged 16 years and over. • People with recurrent upper UTI • People with recurrent lower UTI when underlying cause is unknown. • Pregnant women • Children and young people under 16 • People with suspected cancer	Expert opinion by consensus

ONGOING STUDIES AND RESEARCH GAPS

As of May 16, 2023, no ongoing trial was found on the risk factors for rUTI in adult females.

More studies with higher certainty of evidence are needed in the following areas:

1. comparison of outcomes of therapy of adult female with rUTI who were managed by primary care physicians and those referred to specialists.
2. prognostic factors for rUTI in a population-based sample of women
3. risk factors for complicated urinary tract infection
4. comparison of risk factors for acute sporadic and rUTI

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No studies on the cost-effectiveness of referring adult females with rUTI to specialists were found.

Although UTI remains to be the 3rd leading cause of morbidity in the Philippines [1], there are no local studies on the costs of UTI, much less rUTI. Data for current health expenditure by disease group only includes nephritis among the genito-urinary diseases.[15]

In a health policy agreement funded by the USAID, the Philippine National Health Expenditure Survey results showed urinary system disorders to have the highest share (78%) of out-of-pocket (OOP) payments among the inpatient care health services. The report also showed that as of 2019, medical expenses are still mainly paid OOP,[16] With a high recurrence rate of UTI among women, [2] coupled with a primarily OOP payment of medical care, rUTI imposes considerable financial burden.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

Recurrent UTI among adult females causes not only economic but psychological burden as well. A qualitative study among 29 women with rUTI suggested that rUTI has negative impact on women in terms of taking antibiotics in that they fear the adverse side effects of these drugs and development of antibiotic resistance from taking them. The women in the study also expressed their frustration with the medical profession for underestimating the burden of rUTIs on their lives, including its detrimental impact on their relationships, work, finances, and overall quality of life.[17]

Another observational study done among 575 patients with rUTI showed a correlation between the number of UTI episodes and quality of life, with a lessening of emotional, social, and functional handicaps with decreasing UTI incidence.[7]

REFERENCES

1. DOH Epidemiology Bureau. The 2020 Phil Health Statistics. Available from: https://doh.gov.ph/sites/default/files/publications/2020PHS_FINAL_PDF.pdf
2. Aydin A, Ahmed K, Zaman I, et al. Recurrent urinary tract infections in women. Int Urogynecol J. 2015 Jun;26(6):795-804. doi: 10.1007/s00192-014-2569-5. Epub 2014 Nov 20. PMID: 25410372.

3. Mazzulli T. Diagnosis and management of simple and complicated urinary tract infections (UTIs). Can J Urol. 2012 Oct;19 Suppl 1:42-8. PMID: 23089347.
4. Philippine Society for Microbiology and Infectious Diseases, Philippine Obstetrics and Gynaecology Society, Philippine Society of Nephrology, Philippine Urological Association and Philippine Academy of Family Physicians. Philippine Clinical Practice Guidelines on the Diagnosis and Management of Urinary Tract Infection in Adults 2015 Update: Part 2 Available from: https://thepafp.org/website/wp-content/uploads/2017/05/2015-UTI-Complicated.pdf
5. Hutton A, Amos L, Kerr PG. Investigation and management of recurrent urinary tract infection. Medicine Today 2014; 15(8):33-40 Available from https://medicinetoday.com.au/sites/default/files/cpd/MT2014-08-033-HUTTON_0.pdf
6. Wagenlehner F, Wullt B, Ballarini S, et al. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). Expert Rev Pharmacoecon Outcomes Res. 2018 Feb;18(1):107-117. doi: 10.1080/14737167.2017.1359543. Epub 2017 Jul 31. PMID: 28737469.)
7. Renard J, Ballarini S, Mascarenhas T, Zahran M, Quimper E, Choucair J, Iselin CE. Recurrent Lower Urinary Tract Infections Have a Detrimental Effect on Patient Quality of Life: a Prospective, Observational Study. Infect Dis Ther. 2014 Dec 18;4(1):125–35. doi: 10.1007/s40121-014-0054-6. Epub ahead of print. PMID: 25519161; PMCID: PMC4363217.
8. Naber KG, Tirán-Saucedo J, Wagenlehner FME; RECAP group. Psychosocial burden of recurrent uncomplicated urinary tract infections. GMS Infect Dis. 2022 Mar 24;10:Doc01. doi: 10.3205/id000078. PMID: 35463815; PMCID: PMC9006425.
9. Raz R, Gennesin Y, Wasser J, Stoler Z, Rosenfeld S, Rottensterich E, Stamm WE. Recurrent urinary tract infections in postmenopausal women. Clin Infect Dis. 2000 Jan;30(1):152-6. doi: 10.1086/313596. PMID: 10619744.
10. Haylen BT, Lee J, Husselbee S, Law M, Zhou J. Recurrent urinary tract infections in women with symptoms of pelvic floor dysfunction. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jul;20(7):837-42. doi: 10.1007/s00192-009-0856-3. Epub 2009 Mar 17. PMID: 19495546
11. Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. J Infect Dis. 2000 Oct;182(4):1177-82. doi: 10.1086/315827. Epub 2000 Aug 31. PMID: 10979915
12. Gorter KJ, Hak E, Zuithoff NP, Hoepelman AI, Rutten GE. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. Fam Pract. 2010 Aug;27(4):379-85. doi: 10.1093/fampra/cmq026
13. Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, Stamm WE. Inverse association of H2O2-producing lactobacilli and vaginal Escherichia coli colonization in women with recurrent urinary tract infections. J Infect Dis. 1998 Aug;178(2):446-50. doi: 10.1086/515635. PMID: 9697725
14. Foxman B. Recurring urinary tract infection: incidence and risk factors. Am J Public Health. 1990 Mar;80(3):331-3. doi: 10.2105/ajph.80.3.331. PMID: 2305919; PMCID: PMC1404686.
15. National Institute for Health and Care Excellence. Urinary tract infection (recurrent): antimuicrobial prescribing [Internet]. [London]: NICE; 2018 [cited 2023 May 18]. (NICE guideline [NG112]) https://www.nice.org.uk/guidance/ng112/chapter/Recommendations#referral-and-seeking-specialist-advice
16. Philippine Statistics Authority. The Philippine National Health Accounts 2014-2019. https://psa.gov.ph/sites/default/files/Publication%20PNHA%202019%20signed_1.pdf
17. Javier X, Crosby P, Ross R, et al. Understanding out-of-pocket expenditure for outpatient and inpatient care, Philippine National health Expenditure Survey, Round 1. Washington, DC: US Agency for International Development; 2022 April. Available from http://www.healthpolicyplus.com/ns/pubs/18653-19126_PhilippinesOOP.pdf
18. Scott Victoria C. S., Thum Lauren W., Sadun Taylor et. al. Fear and Frustration among Women with Recurrent Urinary Tract Infections: Findings from Patient Focus Groups. The Journal of Urology 2021 Sept 01 https://doi.org/10.1097/JU.0000000000001843

Applicability Issues

ORGANIZATIONAL CONSIDERATIONS TO IMPLEMENTATION

Although the diagnosis of urinary tract infection is commonly clinical, the use of urinalysis is already widespread in local settings. The abundance of different diagnostic centers, laboratories, and hospitals makes testing using urinalysis practical in the current market. However, what type of urinalysis will be used for screening and diagnostic test would likely differ at the regional, provincial, municipal/city, or even barangay level. The country currently does not have any official standardization of urinalysis test and as such the government and private health sectors operates differently based on the availability, accessibility, cost, and accuracy of the equipment. Thus, the performance of urinalysis and the reporting of its results should be standardized, and the compliance to this standard should be part of the accreditation process of laboratories and hospital by the DOH.

Concerning the current antimicrobial resistance pattern across the country, the use of appropriate treatment might be challenging. One way to ensure optimal and practical treatment is to explore local antibiograms alongside culture sensitivity studies. Patient compliance to treatment should also be taken into consideration, as it helps in slowing down the rate of occurrence of multi-drug resistant bacteria.

For prevention, the use of alternative treatment such as cranberry juice or supplements can be explored. Though it is readily available in groceries across the country, the cost is expensive affecting its accessibility. Therefore, the use of cranberry should be standardized in the formulary as to make it easy for public use.

RESOURCE IMPLICATIONS

The resources available needs to be allocated cost-effectively, as our country has limited resource. The need for using urinalysis as a diagnostic test was discussed with important considerations during the panel meetings for the management of UTI. The use of antibiotic drugs was also deliberated by the panel to ensure appropriate dispensing is done. Local and institutional antibiograms are important resource that could be used to properly prescribed antibiotics. Preventive measures were also considered especially in the recurrence of UTI. Proper health and risk factors assessment would ensure cost-effectiveness.

Regardless, cost, accessibility, and preferences of the available diagnostics and treatment modalities were not considered a significant limitation in the management of UTI. Urinalysis and antibiotic medications are readily available in local drug stores, diagnostic laboratories, online sources, government health institutions, and private hospitals.

Research Implications/Gaps

Despite UTI being a common diagnosis in the country, majority of the recommendations presented in this clinical practice guideline were very low to low certainty of evidence. Some evidence reviewed were indirect, and thus needed assumptions to assess outcomes.

There are no ongoing research studies regarding diagnosis, treatment, and prevention of UTI. This gives us opportunities to study further the research gaps presented in the clinical practice guideline.

For the diagnosis of UTI, the physician typically utilizes their clinical judgement to determine the clinical presentation, severity of the disease, risk factors that can affect the management, and other considerations such as availability of modalities. Therefore, it is important to look further on studies relating to urinalysis to make reliable claims on suggesting and using it as a means for diagnosing UTI.

Common treatment options for UTI are antibiotics and can easily be misused depending on the compliance of the patient or knowledge of the healthcare provider. Although it is noted that there are no ongoing studies with regards to antibiotics for treatment of UTI, there are still existing studies that help us guide on how to use them. Local antibiograms can also be employed as to strengthen treatment recommendations for patients with UTI. Nevertheless, more studies on antibiotic susceptibility, antibiotic use, and harm analysis should be initiated to provide a better opinion on future treatment recommendations.

Although UTI are usually treated with antibiotics, other preventive measures such as cranberry can be used since it is readily available. Granted, the current studies about cranberry are from international setting, it is of great benefit if local studies can be done.

Appendices

Appendix 1. Members of the UTI CPG Task Force

COI REVIEW COMMITTEE

Melo Jane P. Oallarez-Paz, MD

Ms. Suzzette R. Manuel

STEERING COMMITTEE

Marichel D.C Pile-Coronel, MD, FPCP, FPSN
Chair
Adult Nephrology

Ma. Lorna Lourdes Simangan, MD, FPPS, FPSN, FPNSP, MSPH
Vice-Chair
Pediatric Nephrology

Evalyn Roxas, MD, MPH, FPCP, FPSMID
Infectious Diseases Specialist

Ma. Angeles M. Gutierrez-Marbella, MD
Pediatric Nephrology

Carlos Ramon N. Torres, Jr., MD, FPUA, FPCS
Urology

CONSENSUS PANEL

Maaliddin B. Biruar, MD, FPCP, FPSN
Philippine College of Physicians (PCP)

Agnes Avendano Alarilla-Alba, MD
Pediatric Nephrology Society of the Philippines (PNSP)

Violeta V. Meneses-Valderrama, MD, FPPS, FPNSP, FPSN
Pediatric Nephrology Society of the Philippines (PNSP)

Cybele Lara R. Abad, MD, FPCP, FIDSA
Philippines Society for Microbiology and Infectious Diseases (PSMID)

Joseph Adrain L. Buensalido, MD
Philippines Society for Microbiology and Infectious Diseases

Ms. Magnolia Eva Jacinto-Escobedo
Patient Advocate

Ms. Glaiza Postrado
Patient Advocate

Jane Eflyn L. Lardizabal-Bunyi, RPh, MD, OHP, DFM, FPAFP, CSPSH, AFPME, MSc Candidate
Philippine Academy of Family Physicians (PAFP)

Anne Margaret J. Ang, MD
Philippine Society of Nephrology (PSN)

Maria Helen Ferreras Yulde, MD
Philippine Pediatric Society

CONSENSUS FACILITATOR

Pepito E. Dela Peña, MD
National Kidney Transplant Institute

TECHNICAL WORKING GROUP

Ian Theodore G. Cabaluna, RPh, MD, Gdip(ClinEpid), MSc (cand.)
Technical Lead
Institute of Clinical Epidemiology, National Institute of Health
University of the Philippines – Manila

Maria Teresa F. Sanches-Tolosa, MD, D Clin Epi, FPDS
Technical Coordinator
Clinical Epidemiologist

Carolina Linda L. Tapia, MD, MPH
Evidence Review Expert
St. Luke's Medical Center College of Medicine

Gloriosa C. Galindez, MD, FPPS, MPH
Evidence Review Expert
St. Luke's Medical Center College of Medicine

Joanna Marie Uy Tan, RN, MD, DPPS
Evidence Review Expert
Pediatric Infectious Disease and Tropical Medicine Department
San Lazaro Hospital

Marquis Von Angelo Syquio Go Joson, MD, DPPS
Evidence Review Expert

Furqaan Lim, MD, DPPS
Evidence Review Expert

Melissa A. Dator, MD-MBA, DPPS, DPSN, DPNSP
Evidence Review Expert
Division of Pediatric Nephrology, Department of Pediatrics
UP-Philippine General Hospital

Issa Rufina S. Tang, MD, FPCP, FPSMID
Evidence Review Expert
National Kidney Transplant Institute

Esther Uy Tan-Medina, MD, FPPS, FPSN, FPNSP
Evidence Review Expert
Division of Pediatric Nephrology
National Kidney Transplant Institute

Amor Patrice Socorro E. Estabillo, MD, FPCP, FPSN
Evidence Review Expert
Adult Nephrology
National Kidney Transplant Institute

Patricia C. Orduña, MD, FPPS, FCNSP, FPNA
Evidence Review Expert
Division of Pediatric Neurology, Department of Pediatric and Neurosciences
UP-Philippine General Hospital

Rembrandt S. de la Victoria, MD
Technical Writer

ADMINISTRATIVE OFFICER

Mr. Jose Mari Miguel L. Reyes
National Kidney Transplant Institute

Appendix 2. Summary of COI Declarations

Name	Role	Affiliation	Summary of Declared Conflicts of Interest	Assessment
Marichel D.C Pile-Coronel, MD, FPCP, FPSN	Steering Committee	-	None	Participation with no constrains
Ma. Lorna Lourdes Simangan, MD, FPPS, FPSN, FPNSP, MSPH	Steering Committee	-	Secondary Non-Financial Conflict: Chair – Pediatric Nephrology Society of the Philippines Committee; Speaker – Lecture on Pediatric UTI	Manageable with minor constraints
Evalyn Roxas, MD, MPH, FPCP, FPSMID	Steering Committee	-	None	Participation with no constrains
Ma. Angeles M. Gutierrez-Marbella, MD	Steering Committee	-	None	Participation with no constrains
Carlos Ramon N. Torres, Jr., MD, FPUA, FPCS	Steering Committee	-	None	Participation with no constrains
Maaliddin B. Biruar, MD, FPCP, FPSN	Consensus Panel	PCP	None	Participation with no constrains
Agnes Avendano Alarilla-Alba, MD	Consensus Panel	PNSP	None	Participation with no constrains
Violeta V. Meneses-Valderrama, MD, FPPS, FPNSP, FPSN	Consensus Panel	PNSP	None	Participation with no constrains
Cybele Lara R. Abad, MD, FPCP, FIDSA	Consensus Panel	PSMID	None	Participation with no constrains
Joseph Adrain L. Buensalido, MD	Consensus Panel	PSMID	None	Participation with no constrains
Magnolia Eva Jacinto-Escobedo	Consensus Panel	-	None	Participation with no constrains
Glaiza Postrado	Consensus Panel	-	None	Participation with no constrains
Jane Eflyn L. Lardizabal-Bunyi, RPh, MD, OHP, DFM, FPAFP, CSPSH, AFPME, MSc Candidate	Consensus Panel	PAFP	None	Participation with no constrains
Anne Margaret J.	Consensus	PSN	None	Participation

Ang, MD	Panel			with no constrains
Maria Helen Ferreras Yulde, MD	Consensus Panel	PPS	None	Participation with no constrains
Pepito E. Dela Peña, MD	Consensus Facilitator	-	None	Participation with no constrains
Maria Teresa F. Sanches-Tolosa, MD, D Clin Epi, FPDS	Technical Coordinator	-	None	Participation with no constrains
Ian Theodore G. Cabaluna, RPh, MD, Gdip(ClinEpid), MSc (cand.)	Technical Lead	-	None	Participation with no constrains
Carolina Linda L. Tapia, MD, MPH	Evidence Review Experts	-	None	Participation with no constrains
Gloriosa C. Galindez, MD, FPPS, MPH	Evidence Review Experts	-	None	Participation with no constrains
Joanna Marie Uy Tan, RN, MD, DPPS	Evidence Review Experts	-	None	Participation with no constrains
Melissa A. Dator, MD-MBA, DPPS, DPSN, DPNSP	Evidence Review Experts	-	Primary Financial Conflict: Stocks – Makati Medical Center	Manageable with minor constraints
Marquis Von Angelo Syquio Go Joson, MD, DPPS	Evidence Review Experts	-	None	Participation with no constrains
Furqaan Lim, MD, DPPS	Evidence Review Experts	-	None	Participation with no constrains
Issa Rufina S. Tang, MD, FPCP, FPSMID	Evidence Review Experts	-	None	Participation with no constrains
Esther Uy Tan-Medina, MD, FPPS, FPSN, FPNSP	Evidence Review Experts	-	None	Participation with no constrains
Amor Patrice Socorro E. Estabillo, MD, FPCP, FPSN	Evidence Review Experts	-	None	Participation with no constrains
Patricia C. Orduña, MD, FPPS, FCNSP, FPNA	Evidence Review Experts	-	None	Participation with no constrains
Rembrandt S. de la Victoria, MD	Technical Writer	-	None	Participation with no constrains
Jose Mari Miguel L. Reyes	Administrative Officer	-	None	Participation with no constrains