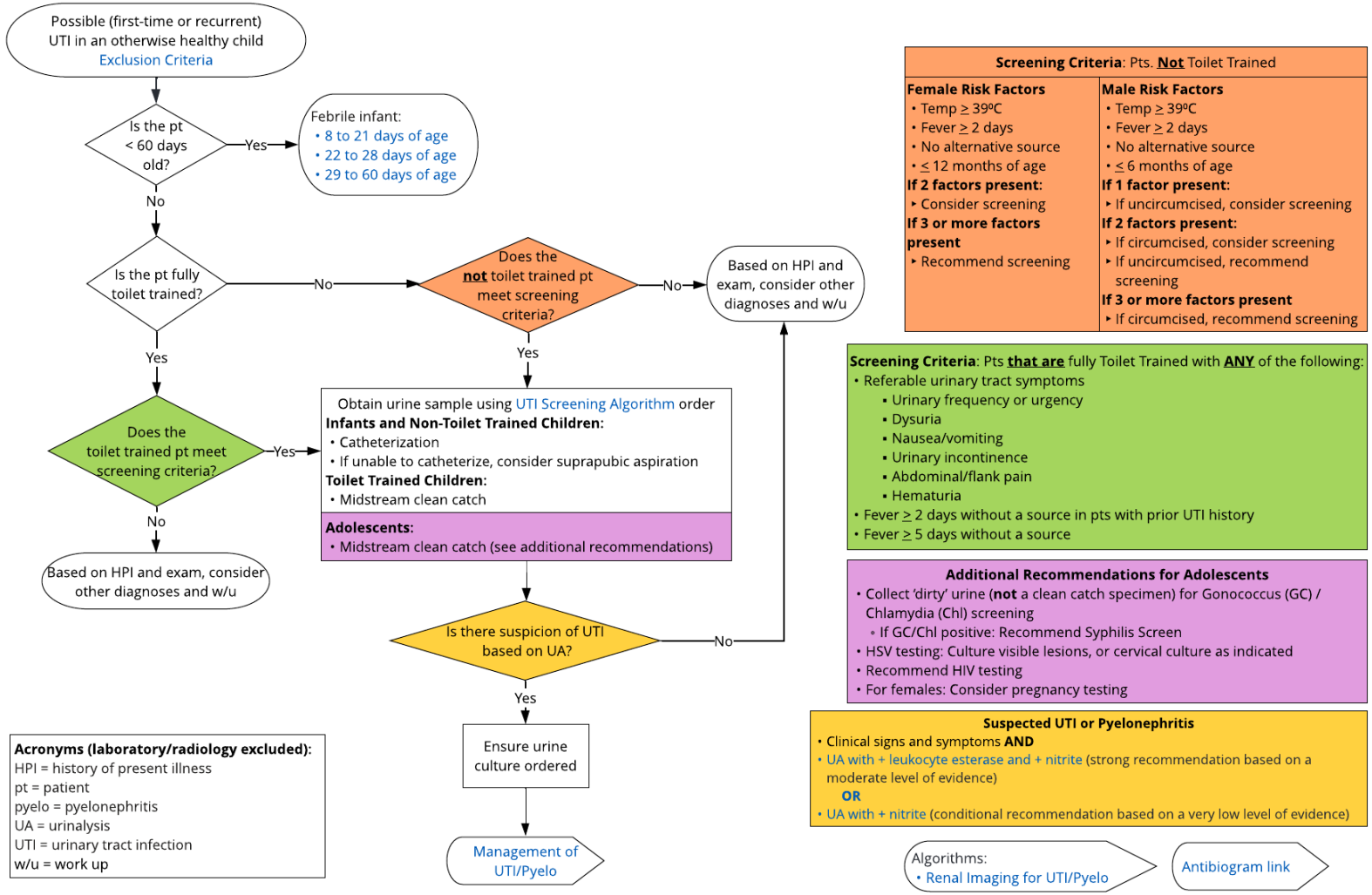
Urinary Tract Infection (UTI) Clinical Practice Guideline (CPG)

Diagnosing Urinary Tract Infections (UTIs)



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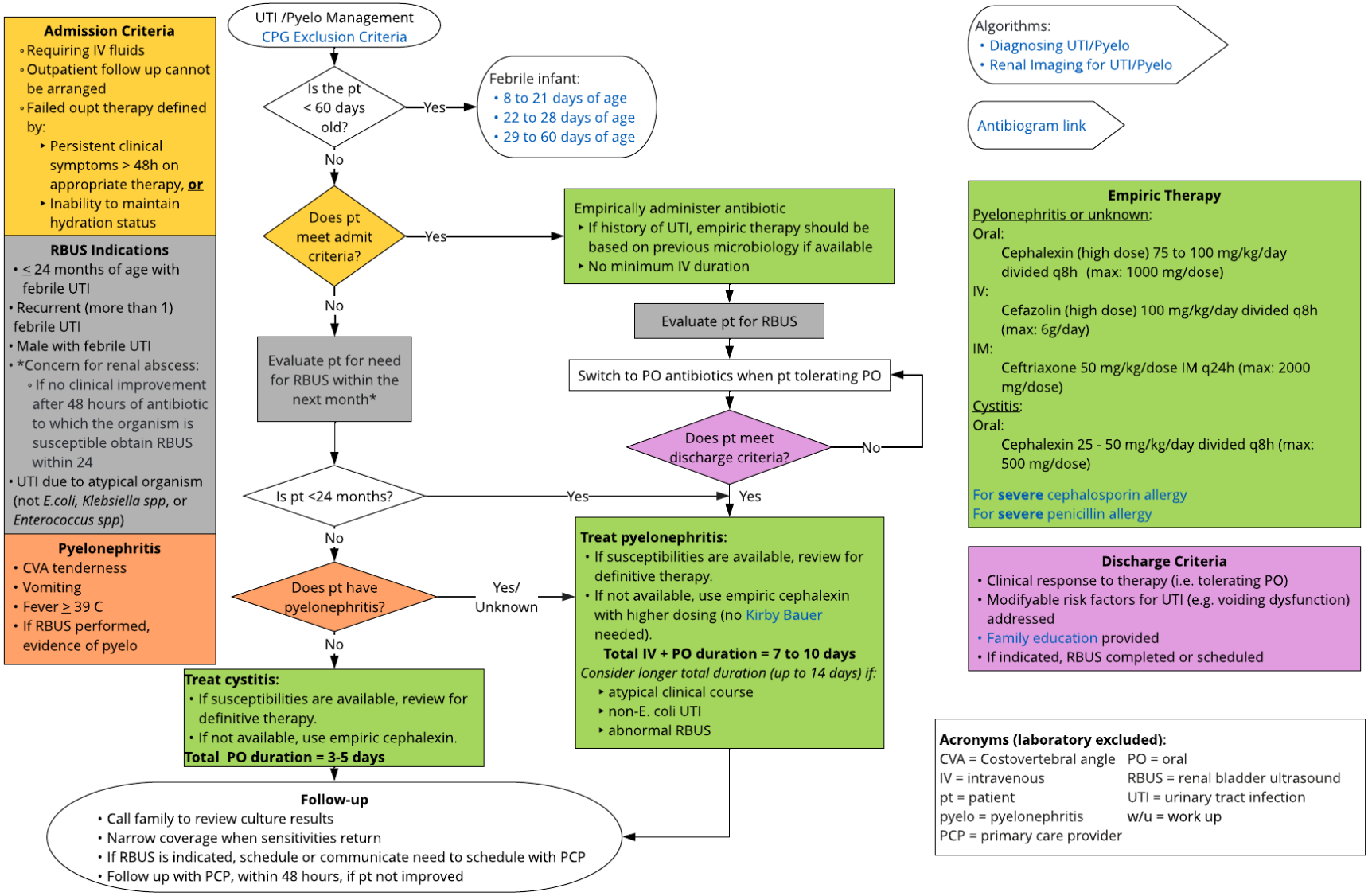
Managing UTI/Pyelonephritis (Inpatient & Outpatient)



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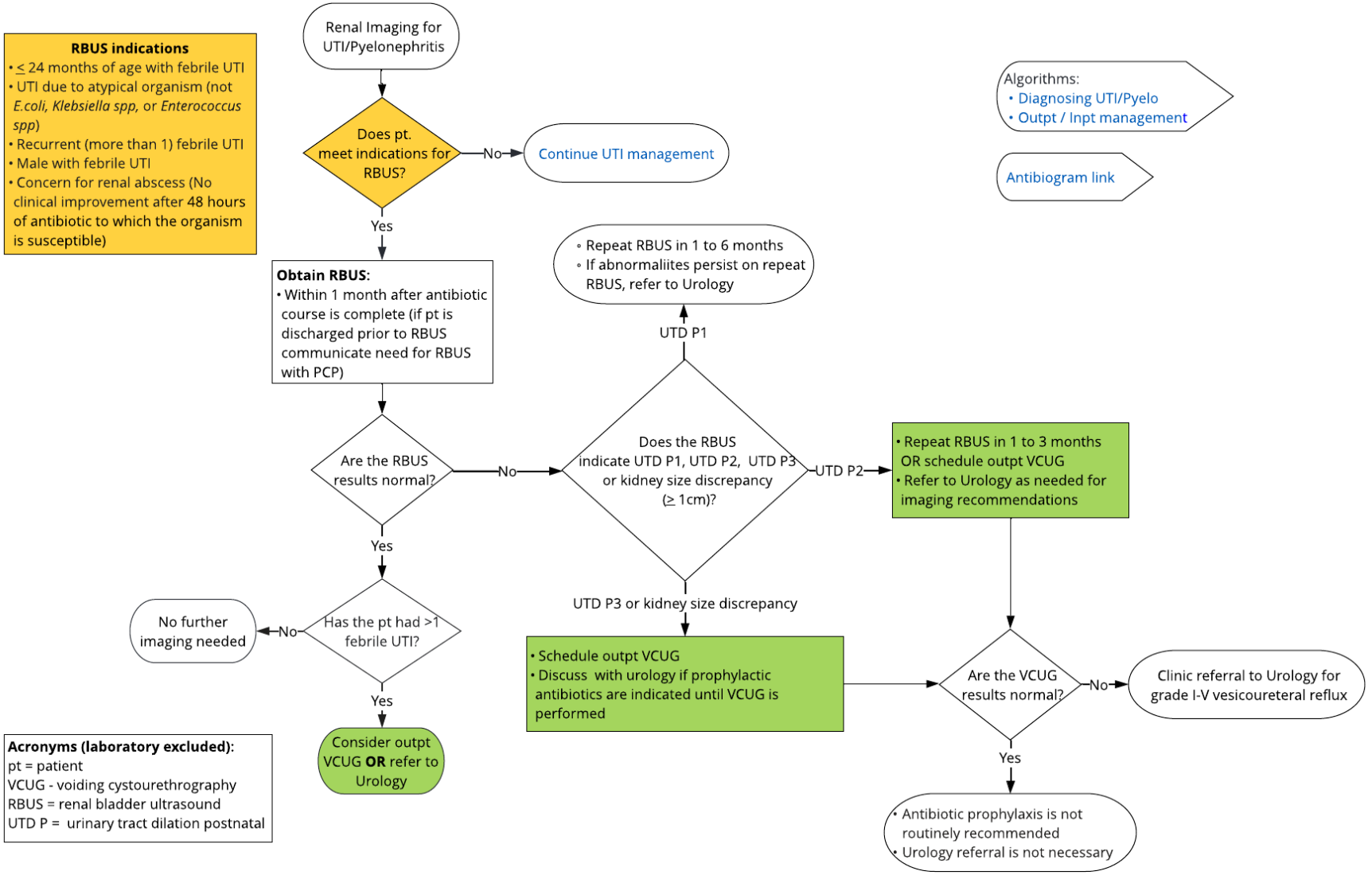
Renal Imaging for UTI/Pyelonephritis



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Guideline Objective

To provide care standards for the otherwise healthy patient 2 months of age or greater with suspected or confirmed first-time or recurrent urinary tract infection (UTI). This guideline was developed to assist clinicians in ambulatory and inpatient settings with the diagnosis, management, and follow-up of patients with UTI or pyelonephritis.

Epidemiology

UTIs are common within the pediatric population and account for nearly 1% of office visits and 5 to 14% of pediatric Emergency Department (ED) visits (Shaikh et al., 2008). Age, toilet training status, sex, comorbidities affecting bowel or bladder function (such as spina bifida, congenital anomalies of the kidney, constipation), and in older children, diabetes, kidney stones, and sexual activity, are all risk factors for UTI.

In the first year of life, UTI is more common in boys (3.7%) compared to 2% in girls (Mattoo et al., 2021). However, after infancy UTI is significantly more prevalent in girls. UTIs are typically caused from colonic bacteria creating infection/inflammation which ascends from the urethra into the bladder. If the inflammatory process is localized to the bladder (cystitis), it is considered a lower UTI; while an upper UTI occurs if inflammation ascends to the ureters and kidneys (pyelonephritis). In otherwise healthy children, the majority (85% to 90%) of UTIs are caused by *Escherichia coli*, while infections with *Klebsiella, Proteus* (more common with stone formation)*, Enterococcus, and Enterobacter* species are less common (Mattoo et al.). Atypical organisms, including *Pseudomonas spp,* group B *Streptococcus, Staphylococcus aureus,* are usually associated with congenital kidney anomalies, genitourinary surgery, or foreign body (such as a catheter) (Mattoo et al.).

Target Users

- Physicians (Ambulatory, Urgent Care, Emergency Department, Hospitalist, Community Physicians, Fellows, and Resident Physicians)
- Advanced Practice Providers
- Nurses

Target Population

Guideline Inclusion Criteria

- > 60 days of age
- Healthy child with possible or confirmed first-time or recurrent UTI

Guideline Exclusion Criteria

- Chronic Kidney Disease
- Suspected or known genitourinary abnormalities, such as (but not limited to): previous genitourinary surgery (other than circumcision), neurogenic bladder or bowel conditions, obstructive uropathy, vesicoureteral reflux
- Septic shock
- Presumed or definite meningitis
- Immunocompromised host
- Pregnancy
- Concern for sexual abuse

AGREE

The American Academy of Pediatrics national guideline (Subcommittee On Urinary Tract Infection, 2016) and the National Institute for Health and Care Excellence (2018) international guideline provided guidance to the CM UTI CPG committee. See Table 1 and 2 for the AGREE II summaries associated with these guidelines.

Table 1
AGREE II[a] Summary for the Subcommittee On Urinary Tract Infection (2016)

Domain	Percent Agreement	Percent Justification
Scope and purpose	81%	The aim of the guideline, the clinical questions posed and target populations **were** identified.
Stakeholder involvement	58%	The guideline **was developed** by the appropriate stakeholders. However, it **did not** include the patient's perspective
Rigor of development	67%	A full description of research methodology was provided in the 2011 guideline. A list of new references is provided with the 2016 reaffirmation. The methodology regarding the level of evidence assessment was not provided. No changes were made to the evidence quality for the individual action statements.
Clarity and presentation	74%	The guideline recommendations **are** clear, unambiguous, and easily identified; in addition, different management options are presented.
Applicability	70%	Barriers and facilitators to implementation, and strategies to improve utilization **were discussed but not clearly addressed** in the guideline. The guideline **did** provide monitoring criteria.
Editorial independence	100%	The recommendations **were not** biased with competing interests.
Committee's recommendation for guideline use	Yes, with modifications	Modifications to this guideline include antibiotics based on Children's Mercy (CM) Hospital antibiogram data and literature related to the use of leukocyte esterase (LE) and nitrite testing.

Note: Four EBP Scholars completed the AGREE II on this guideline.

Table 2
AGREE II[a] Summary for the National Institute for Health and Care Excellence (NICE) (2018)

Domain	Percent Agreement	Percent Justification
Scope and purpose	96%	The aim of the guideline, the clinical questions posed and target populations **were** identified.
Stakeholder involvement	83%	The guideline **was developed** by the appropriate stakeholders and represents the views of its intended users.
Rigor of development	73%	The process used to gather and synthesize the evidence, the methods to formulate the recommendations and to update the guidelines **were** explicitly stated.
Clarity and presentation	86%	The guideline recommendations **are** clear, unambiguous, and easily identified; in addition, different management options are presented.
Applicability	90%	Barriers and facilitators to implementation, strategies to improve utilization and resource implications **were addressed** in the guideline.
Editorial independence	6%	It is **unclear** if the recommendations were biased by competing interests as the authors did not address how conflicts of interest were assessed or managed nor who funded the guideline development.
Committee's recommendation for guideline use	Yes with modifications	Modifications to this guideline include antibiotics based on CM Hospital antibiogram data and literature related to the use of LE and nitrite testing.

Note: Four EBP Scholars completed the AGREE II on this guideline.

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Additional Questions Posed by the CPG Committee

Is Kirby Bauer testing indicated to determine if the *Enterobacter* species is susceptible to cefazolin?

Recommendations from the UTI Clinical Practice Guideline (CPG) Committee

In January 2010, the Clinical and Laboratory Standards Institute (CLSI) published new minimum inhibitory concentration (MIC) breakpoints for cefazolin against Enterobacteriaceae (Wayne, 2010). These new breakpoints were largely based on data from bloodstream infections in adults and do not necessarily reflect increased intrinsic resistance of *E.coli* to cefazolin.

A Kirby Bauer (KB) disk diffusion test can be helpful to identify isolate susceptibility to cefazolin or cephalexin based on these new MIC breakpoints. However, utilizing a higher dose of cefazolin (i.e. 100 – 150 mg/kg/day) or cephalexin (i.e. 75 – 100 mg/kg/day) is likely to overcome intermediate susceptibility for Enterobacteriaceae (e.g *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*) in urinary tract infections, including uncomplicated pyelonephritis.

Therefore, the CMH Urinary Tract Infection Clinical Practice Guideline Committee and subject matter experts recommend higher dose cefazolin or cephalexin without the need for KB disk diffusion in most cases. KB disk diffusion is still recommended for patients who do not respond appropriately to empiric treatment with cefazolin/cephalexin or who are excluded from this guideline (e.g., urologic abnormalities, kidney disease/injury, septic shock, or immunocompromised).

In patients > 2 months of age with signs or symptoms of UTI, what is the Positive Predictive Value (PPV) for leukocyte esterase (LE) or nitrites (alone or in combination) to diagnose a UTI compared to the gold standard of a positive urine culture?

Recommendations from the UTI CPG Committee

- *A conditional recommendation is made for obtaining a urine culture and treating empirically for a UTI if nitrites are positive, based on the GRADE Summary of Findings Table[a] (see page 9). The recommendation is based on a very low level of evidence (see Summary by Outcome for substantiation of recommendations). The overall PPV for nitrites to diagnose a UTI was 84% with a negative predictive value (NPV) of 89%.*
- *A strong recommendation is made for obtaining a urine culture and treating empirically for UTI if nitrites and LE are positive, based on the GRADE Summary of Findings Table[a] (see page 10). The recommendation is based on a moderate level of evidence (see Summary by Outcome for substantiation of recommendations). The overall PPV for LE and nitrites to diagnose a UTI was 93% with a NPV of 94%.*
- *No literature was found that tested the use of LE alone to accurately identify the need to obtain a urine culture and treat empirically for a UTI within the last five years.*

Children's Mercy Practice Recommendations and Reasoning

Children's Mercy adopted a majority of the practice recommendations made by the AAP Clinical Practice Guideline (Subcommittee On Urinary Tract Infection, 2016) and the NICE guideline (2018). However, as a diagnosis is typically made with a combination of clinical signs and symptoms along with abnormal urinalysis, then later confirmed by urine culture, the urinalysis must be correctly obtained and interpreted. Diagnosis is essential to mitigate the acute risks associated with UTI or pyelonephritis, including renal abscess, acute kidney injury, and urosepsis. It is also key in decreasing long-term risks of renal scarring and chronic kidney disease. Hence, the recommendation to obtain a urine culture and treat empirically for UTI if nitrites and LE are positive.

Historically, empiric treatment consisted of a broad-spectrum antibiotic, usually a third-generation cephalosporin. More recent evidence suggests the use of an antibiotic with a narrower spectrum, such as first-generation cephalosporin, is as effective (Daley et al., 2020; Poole et al., 2020). While treatment duration of 7 to 14 days was previously recommended (Roberts, 2011), shorter durations are often appropriate. Shorter duration of narrower agents may decrease the risk of adverse medication effects and antimicrobial resistance while also decreasing healthcare costs (Fox et al., 2020).

Measures

Outcome:

- Proportion of encounters meeting inclusion and diagnosed with UTI who are prescribed an antibiotic for <10-day duration
- Proportion of encounters meeting inclusion who receive empiric cephalexin (oral) or cefazolin (IV)

Process:

- Frequency of use of new antibiotic prescription folders with recommended medication, dose, and duration
- Frequency of use of the new UTI order sets (UCC/ED and Inpatient)

Balancing:

- Return visits to UCC, ED, or inpatient within 14 days

Potential Cost Implications

The following potential improvements may reduce costs and resource utilization for healthcare facilities and reduce healthcare costs and non-monetary costs (e.g., missed school/work, loss of wages, stress) for patients and families.

- Decreased risk of overdiagnosis
- Decreased risk of overtreatment
- Decreased treatment duration
- Decreased unwarranted variation in care
- Decreased risk of antimicrobial resistance

Potential Organizational Barriers and Facilitators

Barriers

- Variability of acceptable level of risk among providers
- Challenges with follow-up faced by some families

Facilitators

- Collaborative engagement across care continuum settings during CPG development
- High rate of use of CPG
- Standardized order set for Urgent Care Clinic, Emergency Department, and Hospital Medicine

Power Plans

- Emergency Department/Urgent Care (see Appendix B)
- Inpatient (see Appendix C)

Guideline Preparation

This guideline was prepared by the Evidence Based Practice (EBP) Department in collaboration with content experts at Children's Mercy Kansas City. The development of this guideline supports the Service and Performance Excellence initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes.

Implementation & Follow-up

Once approved, the guideline was presented to appropriate care teams and implemented. Care measurements will be assessed and shared quarterly with appropriate care teams to determine if changes need to occur.

UTI CPG Committee Members and Representation

- Adrienne DePorre, MD | Hospital Medicine | Committee Chair
- Rana El Feghaly, MD, MSCI | Infectious Diseases | Committee Member
- Allison Hadley, MD | Emergency Medicine | Committee Member
- Amanda Nedved, MD | Urgent Care | Committee Member
- Amol Purandare, MD | Infectious Diseases | Committee Member
- Christine Scoby, DO | Hospital Medicine | Committee Member
- Donna Wyly, MSN, RN, APRN, CPNP-AC, PPCNP-BC, ONC | Urgent Care | Committee Member
- Joel Koenig, MD | Urology | Ad hoc Committee Member

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MIT Committee Members
- Amber Lanning | Provider Clinical Informatics
- Tracy Taylor | Medical Informatics
- George Abraham, MD | Medical Informatics

EBP Committee Members
- Kathleen Berg, MD, FAAP | Evidence Based Practice & Hospital Medicine
- Jacqueline Bartlett, PhD, RN | Evidence Based Practice

Guideline Development Funding

The development of this guideline was underwritten by the following departments/division: EBP, Urgent Care, Infectious Diseases, Emergency Medicine, Hospital Medicine and Urology (Surgery).

Conflict of Interest

If a conflict of interest was identified, the conflict was disclosed and the committee member was excluded from the formulation of a specific recommendation related to the area of conflict. The committee member was allowed to participate in all other guideline development aspects.

Approval Process

This guideline was reviewed, by an internal and external subject matter expert using the AGREE II instrument (see Appendix D). The guideline was approved by the UTI CPG Committee, content expert departments/divisions, and the EBP Department; after which it was approved by the Medical Executive Committee. Guidelines are reviewed and updated as necessary every 3 years within the EBP Department at CMKC. Content expert committees will be involved with every review and update.

Approval Obtained

Department/Unit	Date Approved
Hospital Medicine	March 2, 2022
Emergency Medicine	June 1, 2022
Urgent Care	May 25, 2022
Infectious Diseases	May 19, 2022
Medical Executive Committee	May 4, 2022

Version History

Date	Comments
09/2011	Version one: Utilized AAP UTI guideline
12/2016	Version two: Utilized AAP Reaffirmation UTI guideline
03/2022	Version three: Updated all documents using National Institute for Health and Care Excellence (NICE) (2018) and Subcommittee On Urinary Tract Infection (2016) as foundational guidelines.

Disclaimer

When evidence is lacking or inconclusive, options in care are provided in the guideline and the power plans that accompany the guideline.

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References

Alghounaim, M., Ostrow, O., Timberlake, K., Richardson, S. E., Koyle, M., & Science, M. (2021). Antibiotic Prescription Practice for Pediatric Urinary Tract Infection in a Tertiary Center. *Pediatr Emerg Care*, *37*(3), 150-154. https://doi.org/10.1097/PEC.0000000000001780

Chaudhari, P. P., Monuteaux, M. C., Shah, P., & Bachur, R. G. (2017). The Importance of Urine Concentration on the Diagnostic Performance of the Urinalysis for Pediatric Urinary Tract Infection. *Ann Emerg Med*, *70*(1), 63-71 e68. https://doi.org/10.1016/j.annemergmed.2016.11.042

Coulthard, M. G. (2019). Using urine nitrite sticks to test for urinary tract infection in children aged < 2 years: a meta-analysis. *Pediatr Nephrol*, *34*(7), 1283-1288. https://doi.org/10.1007/s00467-019-04226-6

Daley, M. F., Arnold Rehring, S. M., Glenn, K. A., Reifler, L. M., & Steiner, J. F. (2020). Improving Antibiotic Prescribing for Pediatric Urinary Tract Infections in Outpatient Settings. *Pediatrics*, *145*(4). https://doi.org/10.1542/peds.2019-2503

Doern, C. D., & Richardson, S. E. (2016). Diagnosis of Urinary Tract Infections in Children. *J Clin Microbiol*, *54*(9), 2233-2242. https://doi.org/10.1128/JCM.00189-16

Downs, S. M. (1999). Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. *Pediatrics*, *103*(4), e54. https://doi.org/10.1542/peds.103.4.e54

Fox, M. T., Amoah, J., Hsu, A. J., Herzke, C. A., Gerber, J. S., & Tamma, P. D. (2020). Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. *JAMA Netw Open*, *3*(5), e203951. https://doi.org/10.1001/jamanetworkopen.2020.3951

Kim, H. H., Chung, M. H., Bin, J. H., Cho, K. S., Lee, J., & Suh, J. S. (2018). Urinary YKL-40 as a Candidate Biomarker for Febrile Urinary Tract Infection in Young Children. *Ann Lab Med*, *38*(1), 39-45. https://doi.org/10.3343/alm.2018.38.1.39

Korbel, L., Howell, M., & Spencer, J. D. (2017). The clinical diagnosis and management of urinary tract infections in children and adolescents. *Paediatr Int Child Health*, *37*(4), 273-279. https://doi.org/10.1080/20469047.2017.1382046

Liang, T., Schibeci Oraa, S., Rebollo Rodriguez, N., Bagade, T., Chao, J., & Sinert, R. (2021). Predicting Urinary Tract Infections With Interval Likelihood Ratios. *Pediatrics*, *147*(1). https://doi.org/10.1542/peds.2020-015008

Lo, D. S., Rodrigues, L., Koch, V. H. K., & Gilio, A. E. (2018). Clinical and laboratory features of urinary tract infections in young infants. *J Bras Nefrol*, *40*(1), 66-72. https://doi.org/10.1590/1678-4685-JBN-3602

Mattoo, T. K., Shaikh, N., & Nelson, C. P. (2021). Contemporary Management of Urinary Tract Infection in Children. *Pediatrics*, *147*(2). https://doi.org/10.1542/peds.2020-012138

Nadeem, S., Badawy, M., Oke, O. K., Filkins, L. M., Park, J. Y., & Hennes, H. M. (2021). Pyuria and Urine Concentration for Identifying Urinary Tract Infection in Young Children. *Pediatrics*, *147*(2). https://doi.org/10.1542/peds.2020-014068

National Institute for Health and Care Excellence. (2018). *Urinary Tract Infection in Under 16s: Diagnosis and Management*. https://www.nice.org.uk/guidance/cg54

Poole, N. M., Kronman, M. P., Rutman, L., Weissman, S. J., Migita, R. T., Caglar, D., & Zerr, D. M. (2020). Improving Antibiotic Prescribing for Children With Urinary Tract Infection in Emergency and Urgent Care Settings. *Pediatr Emerg Care*, *36*(6), e332-e339. https://doi.org/10.1097/PEC.0000000000001342

Prah, J. K., Amoah, S., Ocansey, D. W., Arthur, R., Walker, E., & Obiri-Yeboah, D. (2019). Evaluation of urinalysis parameters and antimicrobial susceptibility of uropathogens among out-patients at University of Cape Coast Hospital. *Ghana Med J*, *53*(1), 44-51. https://doi.org/10.4314/gmj.v53i1.7

Roberts, K. B., Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. (2011). 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 128*(3), 595–610. https://doi.org/10.1542/peds.2011-1330

Shaikh, N., Morone, N. E., Bost, J. E., & Farrell, M. H. (2008). Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*, *27*(4), 302-308. https://doi.org/10.1097/INF.0b013e31815e4122

Subcommittee On Urinary Tract Infection. (2016). Reaffirmation of AAP Clinical Practice Guideline: The Diagnosis and Management of the Initial Urinary Tract Infection in Febrile Infants and Young Children 2-24 Months of Age. *Pediatrics*, *138*(6). https://doi.org/10.1542/peds.2016-3026 Trevethan, R. (2017). Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Front Public Health*, *5*, 307. https://doi.org/10.3389/fpubh.2017.00307

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Appendix A: Specific Care Question Measuring the Positive Predictive Value (PPV) for leukocyte esterase (LE) or nitrites (alone or in combination) to diagnose a UTI

Specific Care Question

In patients > 2 months of age with signs or symptoms of a urinary tract infection (UTI), what is the Positive Predictive Value (PPV) for leukocyte esterase (LE) or nitrites (alone or in combination) to diagnose a UTI compared to the gold standard of a positive urine culture?

Recommendations from the UTI Clinical Practice Guideline (CPG) Committee

- *A conditional recommendation is made for obtaining a urine culture and treating empirically for a UTI if nitrites are positive, based on the GRADE Summary of Findings Table[a] (see page 9). The recommendation is based on a very low level of evidence (see Summary by Outcome for substantiation of recommendations). The overall PPV for nitrites to diagnose a UTI was 84% with a negative predictive value (NPV) of 89%.*
- *A strong recommendation is made for obtaining a urine culture and treating empirically for UTI if nitrites and LE are positive, based on the GRADE Summary of Findings Table[a] (see page 10). The recommendation is based on a moderate level of evidence (see Summary by Outcome for substantiation of recommendations). The overall PPV for LE and nitrites to diagnose a UTI was 93% with a NPV of 94%.*
- *No literature was found that tested the use of LE alone to accurately identify the need to obtain a urine culture and treat empirically for a UTI within the last five years.*

Literature Summary

Background

UTIs have been identified as one of the most common bacterial infections in childhood (Korbel et al., 2017; Shaikh et al., 2008). Historically clinicians had tested a urine specimen with a reagent strip that included LE, nitrites, blood, and protein (Downs, 1999). The prevalence of a UTI in febrile infants (greater than 3 months of age) through adolescence ranges from 6.6% to 7.8% (Shaikh et al., 2008). UTIs are difficult to diagnose in the non-verbal child as the clinical presentation can be nonspecific (Doern & Richardson, 2016). The gold standard for diagnosing UTI is a positive urine culture (usually >50,000 CFU of a single uropathogen from a specimen obtained by catheterization, though >10,000 CFU may be appropriate in some clinical scenarios).

Understanding the need to balance testing costs while being antimicrobial stewards, the UTI CPG Committee chose to ascertain if the PPV of LE and/or nitrites could assist care providers in determining which patients should undergo urine culture and receive empiric antimicrobial therapy, thereby reducing unneeded lab testing while still identifying UTIs. This review will summarize identified literature to answer the question posed.

Study characteristics.

The search for suitable studies was completed on September 13, 2021. Rana El Feghaly, MD, MSCI and Adrienne DePorre, MD reviewed the 35 titles and/or abstracts found in the search and identified[b] eight single studies believed to answer the question. After an in-depth review of the single studies[c], six studies answered the question.

Question Answered. Of the included studies, two (Alghounaim et al., 2021; Liang et al., 2021) were retrospective chart reviews, one (Nadeem et al., 2021) was a cross-sectional study, one (Prah et al., 2019) employed prospective random sampling and one (Kim et al., 2018) used case control methodology (see Figure 1). Six of the seven studies enrolled only pediatric patients (Alghounaim et al., 2021; Chaudhari et al., 2017; Kim et al., 2018; Liang et al., 2021; Lo et al., 2018; Nadeem et al., 2021) while Prah et al. (2019) included adults and children with UTIs in their study (mean age = 36 years). Four studies (Alghounaim et al., 2021; Kim et al., 2018; Liang et al., 2021; Prah et al., 2019) measured the PPV of nitrites to diagnose UTIs. Three studies (Alghounaim et al., 2021; Chaudhari et al., 2017; Nadeem et al., 2021) measured the PPV of LE and nitrites to diagnose UTIs. No studies were identified that measured the PPV of LEs to diagnose UTIs. Of the six studies analyzed, three studies (Alghounaim et al., 2021; Kim et al., 2018; Prah et al., 2019) had a prevalence significantly higher (51%, 56%, and 30%, respectively) than the reported prevalence established by Shaikh et al. (2008) which ranged from 6.6% to 7.8%.

Summary by Outcome
Data Summary by Outcome (rationale for evidence certainty rating[a] provided for each outcome)
PPV of Nitrites
Four studies (Alghounaim et al., 2021; Kim et al., 2018; Liang et al., 2021; 3129-Prah et al., 2019) measured the PPV of nitrites to identify a UTI (*n* = 2610). The overall PPV for nitrites to diagnose a UTI was 84% with a NPV of 89%. It is important to note that as the prevalence of UTI decreases the PPV decreases as there are more false positives for every true positive (Trevethan, 2017). Additionally, the NPV increases because there are more true negatives for every false negative (Trevethan, 2017). The prevalence of UTI for the four included studies was 13%. However, based on Shaikh et al. (2008) published prevalence of 7%, the use of Nitrites would result in 40 to 55 false negatives per 1000 patients (see Table 1). The sensitivity and specificity for positive nitrites to identify UTI were 84% and 89%, respectively. See the Summary Receiver Operating Curve (SROC), Figure 3, for this outcome.

> **Certainty of the Evidence for Nitrites to Diagnosis a UTI.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have any imprecision concerns. However, the evidence did have serious risk of bias, serious indirectness, and serious inconsistency issues. Risk of bias was serious as four studies were judged to be high risk for patient selection and the reviewers were unable to ascertain if the flow and timing affected the results due to the exclusion of some patients. Indirectness was judged to be serious as three (Alghounaim et al., 2021; Kim et al., 2018; Prah et al., 2019) of the studies reported higher UTI prevalence (30%, 51%, 56%) than the range of 6.6% to 7.8% reported in an epidemiologic study (Shaikh et al., 2008). Inconsistency was judged to be serious as the CIs for sensitivity did not overlap (see Figure 5).

PPV of LE and Nitrites
Three studies (Alghounaim et al., 2021; Chaudhari et al., 2017; Nadeem et al., 2021) measured the PPV of LE and nitrites to identify a UTI (*n* = 39,316). The overall PPV for LE and nitrites to diagnose a UTI was 93% with a NPV of 94%. The prevalence of UTI for the combined studies was 8%. Therefore the use of LE and Nitrites would result in 52 to 54 false negatives per 1000 patients (see Table 2). The sensitivity and specificity for the use of LE and nitrites were 33% and 100%, respectively. See the SROC (Figure 4) for this outcome.

> **Certainty of the Evidence for LE and Nitrites to Diagnose a UTI.** The certainty of the body of evidence was moderate. The body of evidence was assessed to not have serious inconsistency, indirectness, or imprecision. However, the body of evidence was judged to have serious risk of bias issues. Two (Alghounaim et al., 2021; Chaudhari et al., 2017) of the studies were judged to be high risk for patient selection and the reviewers were unable to ascertain if the flow and timing affected the results due to the exclusion of some patients. Alghounai et al. (2021) reported the prevalence of UTIs in their patient population to be 51% which was significantly higher than the reported range (6.6% to 7.8%) in Shaikh et al. (2008) epidemiologic study. The other two studies (Chaudari, 2017; and Nadeem, 2021) reported a prevalence of 8%. As Alghounai's sample size was 179 and the combined sample size of the other studies (Chaudari, 2017; and Nadeem, 2021) equaled 39,137, imprecision was not downgraded.

Identification of Studies
Search Strategy and Results (see Figure 1)
Search Strategy: "Urinary Tract Infections/diagnosis"[Majr] AND ((("Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Positive Predictive Value") AND ("leukocyte esterase" or nitrite)) OR (("Urinary Tract Infections/microbiology"[Mesh] OR "urine culture") AND ("leukocyte esterase" or nitrite))) AND (child OR children OR infant OR pediatr* OR paediatr* OR adolescence); Filter applied: last five years.
Records identified through database searching *n* = 30
Additional records identified through other sources *n* = 5

Studies Included in this Review

Citation	Study Type
Alghounaim et al. (2021)	Retrospective cohort
Chaudhari et al. (2017)	Retrospective cohort
Kim et al. (2018)	Case Control
Liang et al. (2021)	Retrospective cohort
Nadeem et al. (2021)	Cross-sectional
Prah et al. (2019)	Prospective random sampling

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Coulthard (2019)	Author recalculated sensitivity and specificity
Lo et al. (2018)	Study population were infants < 3 months of age, the median age (SD) was 1.5 months (0.7)

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[d]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[d]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

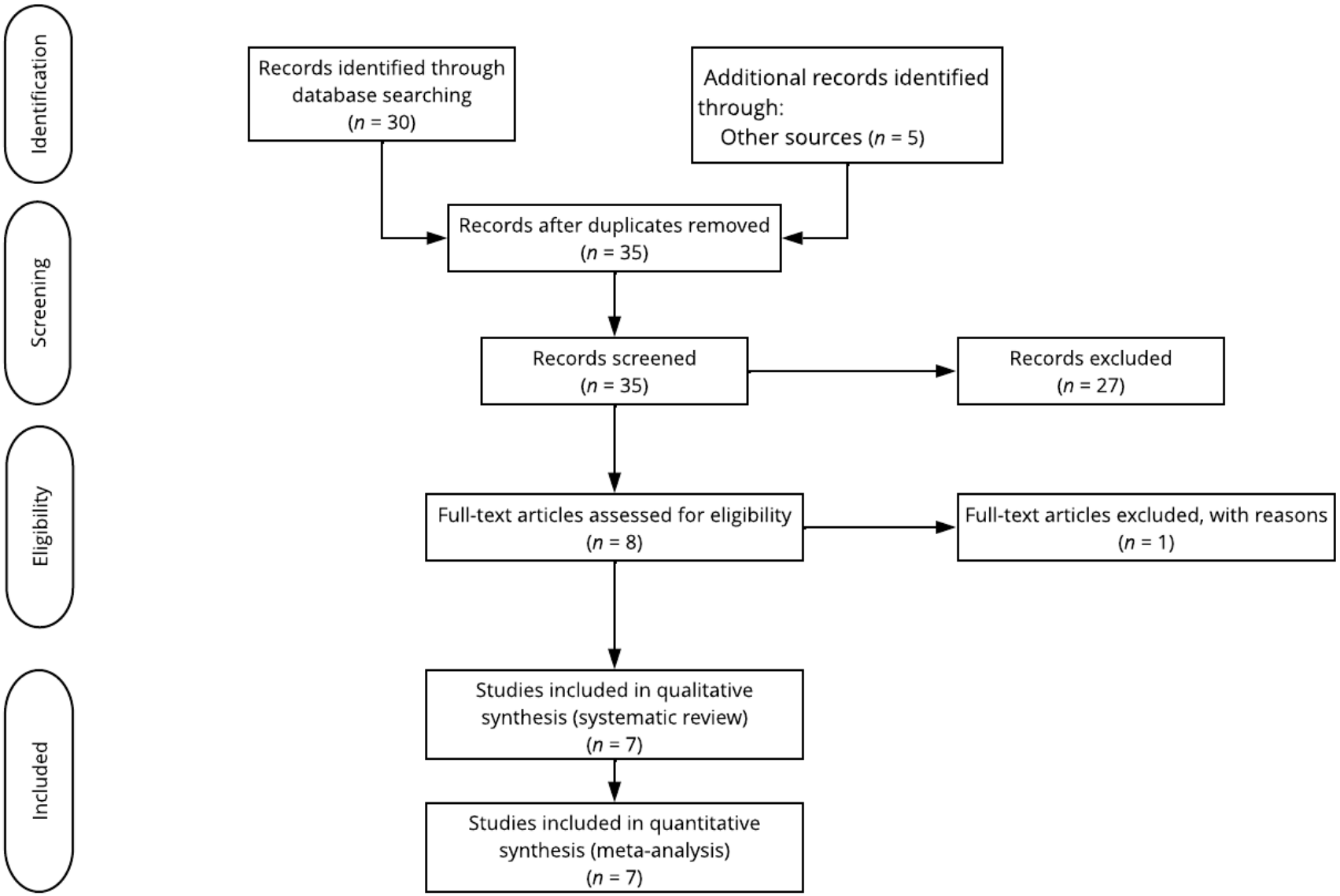
Acronym	Explanation
CAT	Critically Appraised Topic
CFU	Colony forming units
EBP	Evidence Based Practice
ED	Emergency Department
LE	Leukocyte esterase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UTI	Urinary Tract Infection

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
CI	Confidence Interval
n	Number of cases in a subsample
N	Total number in sample
NPV	Negative Predictive Value
PPV	Positive Predictive Value
RCT	Randomized controlled trial
SR	Systematic Review
SROC	Summary Receiver Operating Curve

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[d]



** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interest of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Figure 2
Summary Risk of Bias and Applicability Concerns

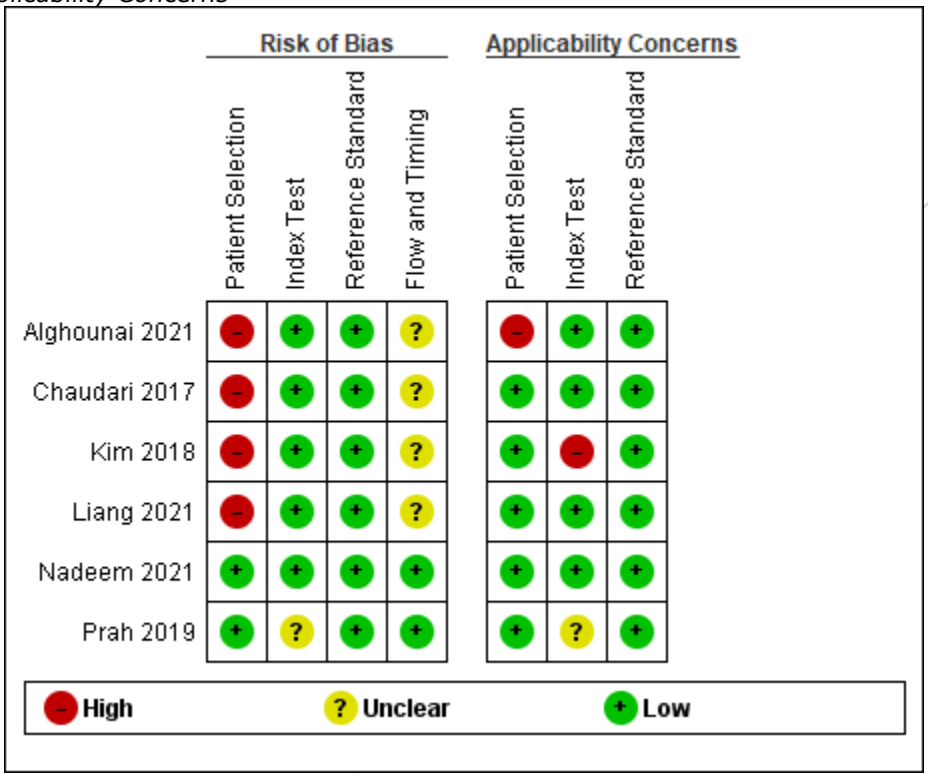


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Figure 3
SROC for Nitrites (+) Data

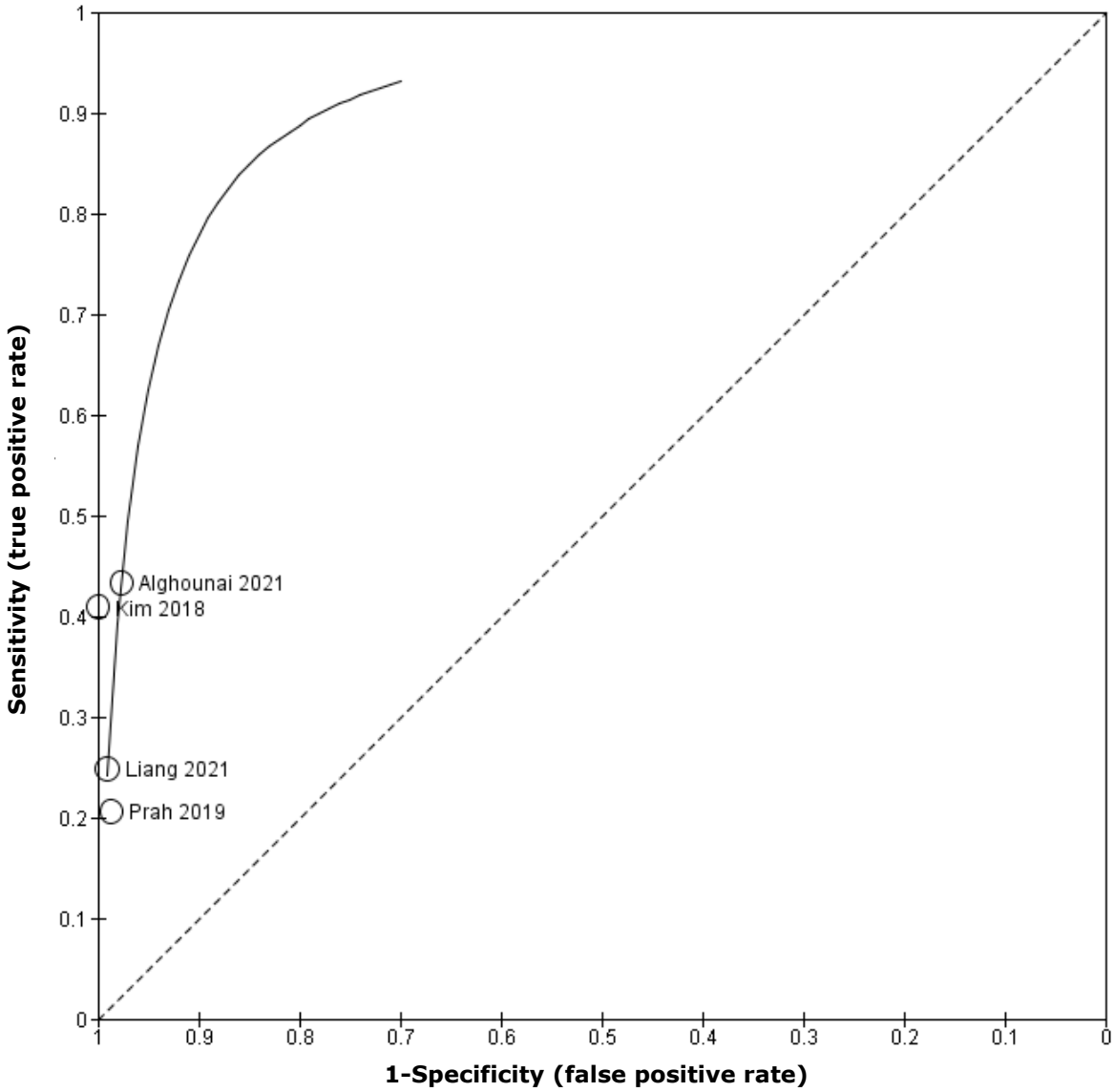

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Figure 4
SROC for LE (+) and Nitrites (+) Data

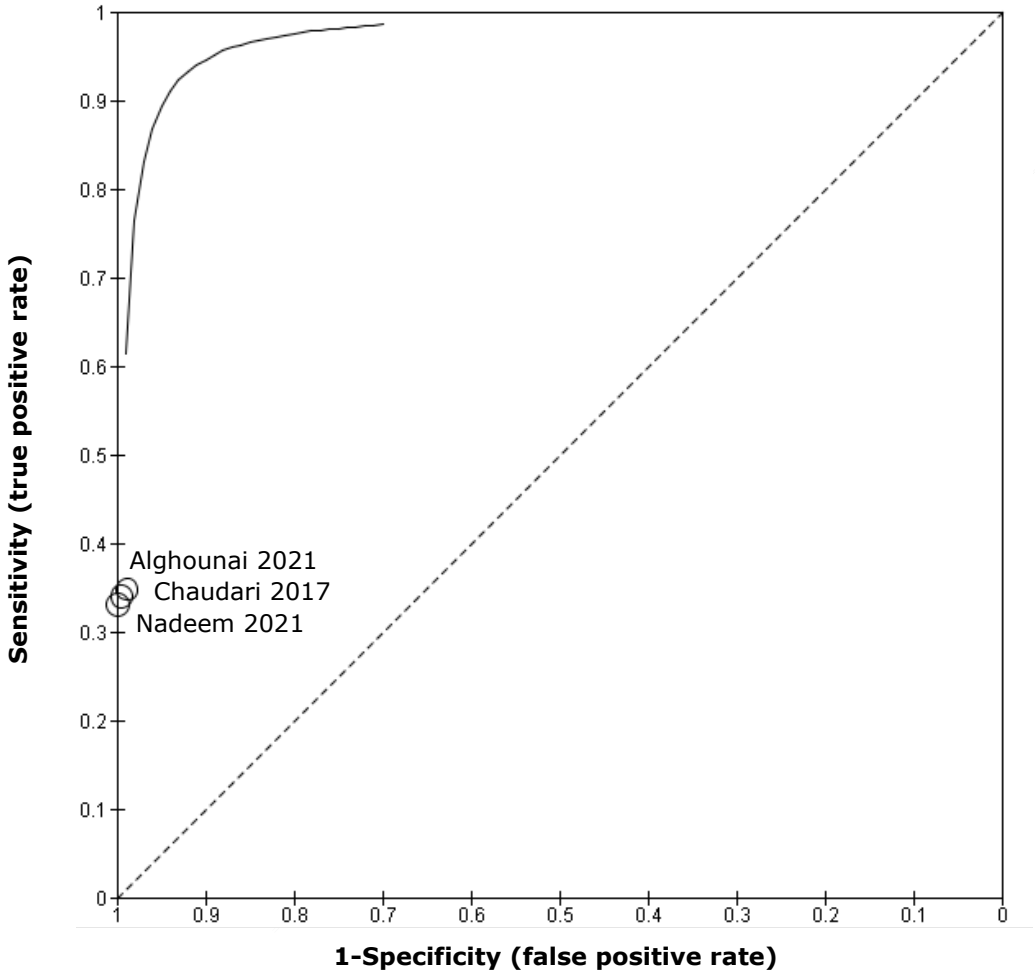


Table 1.

Summary of Findings Table: Should Nitrite (+) be used to diagnose UTI in pts > 2 months of age to adolescence?

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease Certainty of Evidence (CoE)					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirect-ness	Inconsis-tency	Impre-cision	Publi-cation bias	pre-test probability of 7%	pre-test probability of 15%	pre-test probability of 30%	
True positives (patients with UTI)	4 studies 394 patients	cohort & case-control type studies	serious[a]	not serious	serious[b]	serious[c]	none	15 to 30	32 to 65	63 to 129	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having UTI)								40 to 55	85 to 118	171 to 237	
True negatives (patients without UTI)	4 studies 2216 patients	cohort & case-control type studies	serious[a]	not serious	not serious	serious[c]	none	911 to 930	833 to 850	686 to 700	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having UTI)								0 to 19	0 to 17	0 to 14	

Explanations

a. Pt selection from four studies were identified to be high risk. Unclear risk was attributed to the characteristic of flow and timing.

b. Sensitivity data was identified to be inconsistent among the four studies.

c. Three of the five studies reported a higher prevalence value (30%, 51%, 56%) than reported in an epidemiologic study (6.6% to 7.8%).

Table 2.

Summary of Findings Table: Should LE (+) and Nitrite (+) be used to diagnose UTI in pts > 2 months of age to adolescence?

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease Certainty of Evidence (CoE)					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirect-ness	Inconsis-tency	Impre-cision	Publication bias	pre-test probability of 8%	pre-test probability of 30%	pre-test probability of 50%	
True positives (patients with UTI)	3 studies 3250 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious[b]	none	26 to 28	99 to 105	165 to 175	⊕⊕⊕◯ Moderate
False negatives (patients incorrectly classified as not having UTI)								52 to 54	195 to 201	325 to 335	
True negatives (patients without UTI)	3 studies 36066 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious[b]	none	911 to 920	693 to 700	495 to 500	⊕⊕⊕◯ Moderate
False positives (patients incorrectly classified as having UTI)								0 to 9	0 to 7	0 to 5	

Explanations

a. Two of the three studies were judged to have a high risk of bias. Alghounai (2021) sample size was n = 179, while the other (Chaudari, 2017) had a sample size of n = 14967

b. The prevalence of UTI in Alghounai (2021) was 51% which was significally higher than than the reported range (6.6% to 7.8%) in epidemiologic studies. However, the other two studies (Chaudari, 2017; and Nadeem, 2021) reported a UTI prevalence of 8%. As Alghounai's sample size was 179 and the combined sample of the other studies (Chaudari, 2017; and Nadeem, 2021) equaled 39,137, imprecision was not downgraded.

Meta-analyses

Figure *5*

Nitrites (+) for All Specimens (Combined Catheterized and Clean Catch)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alghounai 2021	39	2	51	83	0.43 [0.33, 0.54]	0.98 [0.92, 1.00]
Kim 2018	18	0	26	35	0.41 [0.26, 0.57]	1.00 [0.90, 1.00]
Liang 2021	49	19	148	1928	0.25 [0.19, 0.32]	0.99 [0.98, 0.99]
Lo 2018	20	0	45	454	0.31 [0.20, 0.43]	1.00 [0.99, 1.00]
Prah 2019	13	2	50	147	0.21 [0.11, 0.33]	0.99 [0.95, 1.00]

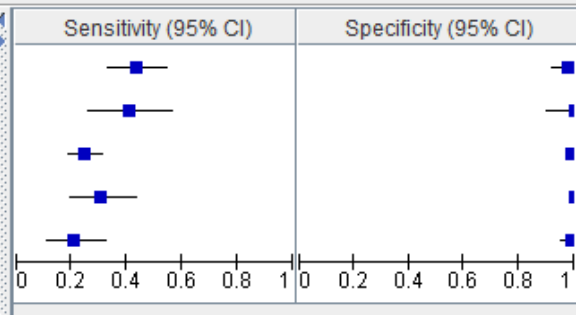
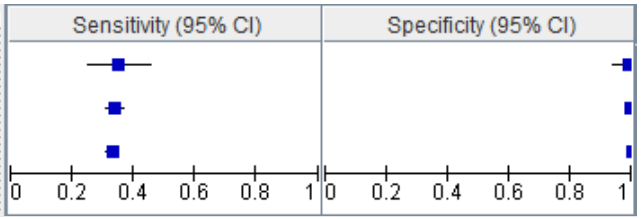


Figure *6*

LE (+) and Nitrites (+) for All Specimens (Combined Catheterized and Clean Catch)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alghounai 2021	32	1	60	86	0.35 [0.25, 0.45]	0.99 [0.94, 1.00]
Chaudari 2017	391	75	761	13740	0.34 [0.31, 0.37]	0.99 [0.99, 1.00]
Nadeem 2021	664	12	1342	22152	0.33 [0.31, 0.35]	1.00 [1.00, 1.00]



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Characteristics of Diagnostic Studies
Alghounaim et al. (2021)
Patient Selection

A. Risk of Bias	
Patient Sampling	**Methods:** Retrospective Chart Review **Number Enrolled:** N = 183 **Age Median (IQR):** 4.2 years (1.1-7.5) **Gender, Male (%):** *n* = 32 (17.4) • 292 patients were discharged from Emergency Department (ED) with diagnosis of UTI **Subjects excluded from study with rationale** *n* = 110 patients based in criteria • 26 were admitted • 25 urine culture results were not available (either not ordered [*n* = 10] or done elsewhere [*n* = 15]) • 23 had underlying genitourinary tract abnormalities • Two were on UTI prophylaxis • Six were transferred to another institution • Three were duplicate • Six were younger than 12 weeks • Seven had conditional antibiotic prescription • 12 had urine cultures done on therapeutic antibiotics **Race/Ethnicity:** not disclosed
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** Single center, at the Hospital of Sick Children (Toronto, Ontario, Canada) **Timeframe:** October to December 2016. **Inclusion:** • Patients 12 weeks to younger than 18 years • Discharged from the ED with the diagnosis of UTI. **Exclusion:** • Younger than 12 weeks • Underlying genitourinary tract abnormalities • Admitted or transferred to another center • Receiving antibiotics on presentation • Urine testing done in another laboratory • Received a conditional prescription to be filled if the urine culture was positive • Duplicate occurrences (>1 ED visit within the same illness period) **Prevalence (calculated by review author):** • All Specimens: 51.4% • Catheter Specimens: 71.7% • Noncatheter Specimens: 41.2%

Are there concerns that the included patients and setting do not match the review question?	High concern

Index test

Index tests	• Leukoctye Esterase (LE), sensitivity 5–15 white blood cells (WBC)/high power field ○ The semi-quantitative results of LE were trace, small (+1), moderate (+2), and large (+3) that corresponded to 15, 75, 125, and 500 WBC/high power field, respectively • Urinary Nitrites, sensitivity 13–22 umol/L Clinitek Status (Siemens Healthcare, Munich, Germany)

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interest of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Reference Standard

Target condition and reference standard(s)	• Confirmed UTI was defined as pyuria and the presence of more than 50,000 CFU/mL (>50,106 CFU/L) of 1 or more uropathogen • In addition, presence of more than 50,000 CFU/mL of a uropathogen along with less than 50,000 CFU/mL of nonuropathogen was considered significant growth • Unconfirmed UTI included patients with a negative urine culture that was defined as cultures that failed to show bacterial growth after 24 hours, had growth of less than 50,000 CFU/mL, or had significant but mixed growth of more than 1 organism other than a typical uropathogen. In addition, growth of a uropathogen and a nonuropathogen, both greater than 50,000 CFU/mL, was considered to result from contamination
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Test done at the same time. Urine culture had to wait on growth. • 292 patients were discharged from ED with diagnosis of UTI, the study excluded 110 of these patients (see exclusion criteria) • 25 urine culture results were not available (either not ordered [*n* = 10] or done elsewhere [*n* = 15])
Was there an appropriate interval between index test and reference standard?	Yes

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Chaudhari et al. (2017)
Patient Selection

A. Risk of Bias	
Patient Sampling	**Method:** Retrospective Chart Review **Number enrolled:** *N* = 14,971 **Subjects excluded from study with rationale** *n* = 1,654 **Age, median (IQR):** 1.5 years (0.4, 5.5) **Gender, Male (%):** *n* = 5,988 (40%) **Race/Ethnicity:** • white= 40.5% • Hispanic = 16.3% • African American = 14.4% • Asian American = 4.4% • Other = 18.1% • Unknown = 6.3%
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** Single-center, ED **Timeframe:** May 2009 and December 2014 **Inclusion:** • Patients younger than 13 years of age • Evaluated for UTI • Children who had a urine dipstick or micro-urinalysis and a paired urine culture **Exclusion:** • Urine culture yielded multiple urogenital organisms • Nonpathogenic organisms • Urine culture was obtained from a urine bag • Indwelling urinary catheter • Urine source was missing • Specific gravity was missing **Prevalence (reported by authors):** 7.7%
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index test

Index tests	• Leukocyte Esterase (trace was considered positive) and Nitrites via urine dip stick and categorized by specific gravity

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

Target condition and reference standard(s)	• For urine specimens obtained by urethral catheterization, positive urine culture was defined by a single urinary pathogen greater than or equal to 50,000 CFU/mL. • For urine specimens obtained by standard midstream "clean catch," a positive urine culture for male patients was defined as having a single urinary pathogen greater than or equal to 50,000 CFU/mL; for female patients, greater than or equal to 100,000 CFU/mL.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	• Test done at the same time. Urine culture had to wait on growth. • Patients that did not get the reference standard were excluded from the study.
Was there an appropriate interval between index test and reference standard?	Yes

Did all patients receive the same reference standard?	Yes

Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

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Notes	At the study institution, if a dipstick testing result is negative, microscopic urinalysis is not routinely performed. If the patient had a paired dipstick and urine culture without a microscopic urinalysis, a negative dipstick result was considered equivalent to a negative microscopic urinalysis result.

Kim et al. (2018)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Method:** Case-control **Number enrolled:** *N* = 79 **Age, mean (SD):** • **Case group:** 6.30 years (4.77) • **Control group:** 6.71 years (2.74) **Gender, Male (%):** • **Case group:** *n* = 28 (63.6%) • **Control group:** *n* = 19 (54.3%) **Race/Ethnicity:** not disclosed
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** Inpatients at the Catholic University of Korea, Bucheon St. Mary's Hospital **Timeframe:** March 2013 through January 2015 **Inclusion criteria:** • **Case group:** Febrile children with a positive urine culture, obtained from a catheterized specimen, which had pure growth of 100,000 CFU/mL, *n* = 44 • **Control group:** Febrile children with a negative urine culture (how the specimen was obtained was not reported by the authors), *n* = 35 **Exclusion criteria:** • Febrile children administered antibiotics before visiting the hospital were excluded **Prevalence (calculated by reviewer):** 55.7%
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index test

Index tests	• YKL-40 (inflammatory marker) levels were obtained upon routine urine collection for culture • Samples were centrifuged at 4°C for 15 minutes at 3,000xg within 30 minutes of collection and stored at -80°C until final analyses. Samples were tested in duplicate and mean values were presented.

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Reference Standard

Target condition and reference standard(s)	• Febrile children with positive urine culture results showing pure growth of 100,000 CFU/mL
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	• Tests done at the same time. • Urine culture had to wait on growth.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk
Notes	Urine nitrites were only reported in the pts that had a (+) urine culture.

Liang et al. (2021)
Patient Selection

A. Risk of Bias	
Patient Sampling	**Method:** Retrospective Chart Review **Number Enrolled:** *N* = 2144 **Subjects excluded from study with rationale:** *n* = 712 • Non-ED testing, *n* = 555 • No matched urinalysis, *n* = 157 • Contaminants or asymptomatic or insignificant bacteriuria, *n* = 141 **Age, median (IQR):** 1.5 years (0.4, 5.5) **Gender, Male (%):** *n* = 1029 (48%) **Race/Ethnicity (calculated by review author):** • African American = 85% • Hispanic = 6% • Asian American = 2% • white = 1% • Other = 6%
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** Single-center ED, Brooklyn, New York **Timeframe:** December 2011 to December 2019. **Inclusion:** • Children < 2 years of age • Urinalysis and urine culture sent **Exclusion:** • Urine culture was sent without a urinalysis in the same visit • Urine testing was not sent from the pediatric ED **Prevalence (reported by author):** 9.2%
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index test

Index tests	Leukocyte esterase • LE were reported by the hospital laboratory as negative, trace, 1+, 2+, and 3+ • Positive was considered any level Nitrites • Nitrites were measured as positive or negative

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

Target condition and reference standard(s)	• UTI was defined per the American Academy of Pediatrics (AAP) guidelines, which require evidence of pyuria or bacteriuria on urinalysis and >50 000 colony-forming units per mL of a pathogenic bacteria in urine culture from a sterilely obtained sample.
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	• Tests done at the same time. Urine culture had to wait on growth. • Patients that did not get the reference standard were excluded from the study
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

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Notes	• The providers' clinical reasoning to send urine was not used as selection criteria to include the widest range of patient presentations. • Urine collection method not reported.

Nadeem et al. (2021)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Method:** Retrospective cross-sectional study **Number Enrolled:** N = 24,171 **Participants prior to inclusion/exclusion criteria screening:** N = 30,462 **Subjects excluded from study with rationale:** n = 6,291 **Age, median (IQR):** 7.3 months (2.5–12.9 months) **Gender, Male (%):** 9955 (41.2) **Race/Ethnicity:** • Hispanic = 54.5% • white = 21.1% • African American = 17.5% • Asian American = 2% • Other = 3.1% • Unknown = 1.8%
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** ED of a quaternary children's hospital in Texas **Timeframe:** between January 2012 and December 2017 **Inclusion criteria:** • Children < 24 months of age with suspected UTI • Paired urinalysis and urine culture obtained **Exclusion criteria:** • Patients with >1 ED visit, data from second and subsequent visits were excluded • Patients with unknown urine collection source, indwelling catheter, bag urine, missing urinalysis results, urine culture growing mixed or multiple organisms or normal genital flora, or missing colony counts **Prevalence (calculated by reviewer):** 8.3%
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index test

Index tests	Identification of WBCs per high-power field cutoff for microscopic pyuria at three urine specific gravity groups: • low <1.011 • moderate 1.011–1.020 • high>1.020 in predicting a positive urine culture result

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

Target condition and reference standard(s)	• Transurethral in-and-out catheterization specimens with growth of >50,000 CFU/mL of a single uropathogen were defined as positive.
	• Standard midstream specimens were positive if >100,000 CFU/mL of a single uropathogen grew in culture.
	• For this study, pathogenic urogenital organisms included
	  ○ Escherichia coli,
	  ○ Proteus species,
	  ○ Klebsiella species,
	  ○ Serratia marcescens,
	  ○ Citrobacter species,
	  ○ Enterobacter species,
	  ○ Pseudomonas species,
	  ○ Enterococcus species,
	  ○ Streptococcus agalactiae, and
	  ○ Staphylococcus saprophyticus.
	• Urine cultures with growth of multiple organisms or urogenital flora were interpreted as contaminated specimens and were excluded from the study analysis.

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

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Flow and Timing

A. Risk of Bias		
Flow and timing	Tests done at the same time. Urine culture had to wait on growth.	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk

Prah et al. (2019)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Methods:** Prospective Random Sampling **Number Enrolled:** *N* = 213 • UTI patients: *n* = 64 **Age, mean (Range):** • UTI patients 36.62±17.4 years (9-73 years) • non-UTI patients age not reported **Gender, Male (%):** • UTI patients: *n* = 16 (25%) **Race/Ethnicity:** not disclosed
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Setting:** Single-center Outpatient Clinics, University of Cape Coast Hospital, Ghana **Timeframe:** July 2017 – December 2017 **Inclusion:** • Suspected cases of UTI for urinalysis **Exclusion:** • Urinary obstruction • Urinary retention caused by neurological disease • Immunosuppression • Pregnancy • Presence of foreign bodies such as calculi, indwelling catheters or other drainage devices • If a patient had taken antibiotics within two weeks prior to the study.

	Prevalence (reported by authors): 30.0%
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index test

Index tests	Nitrites test Leukocyte esterase test Presence of urinary pus cells ≥ 5 per HPF • Dipstick urinalysis was done using Combur 10-Test M strips with reagent pads

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

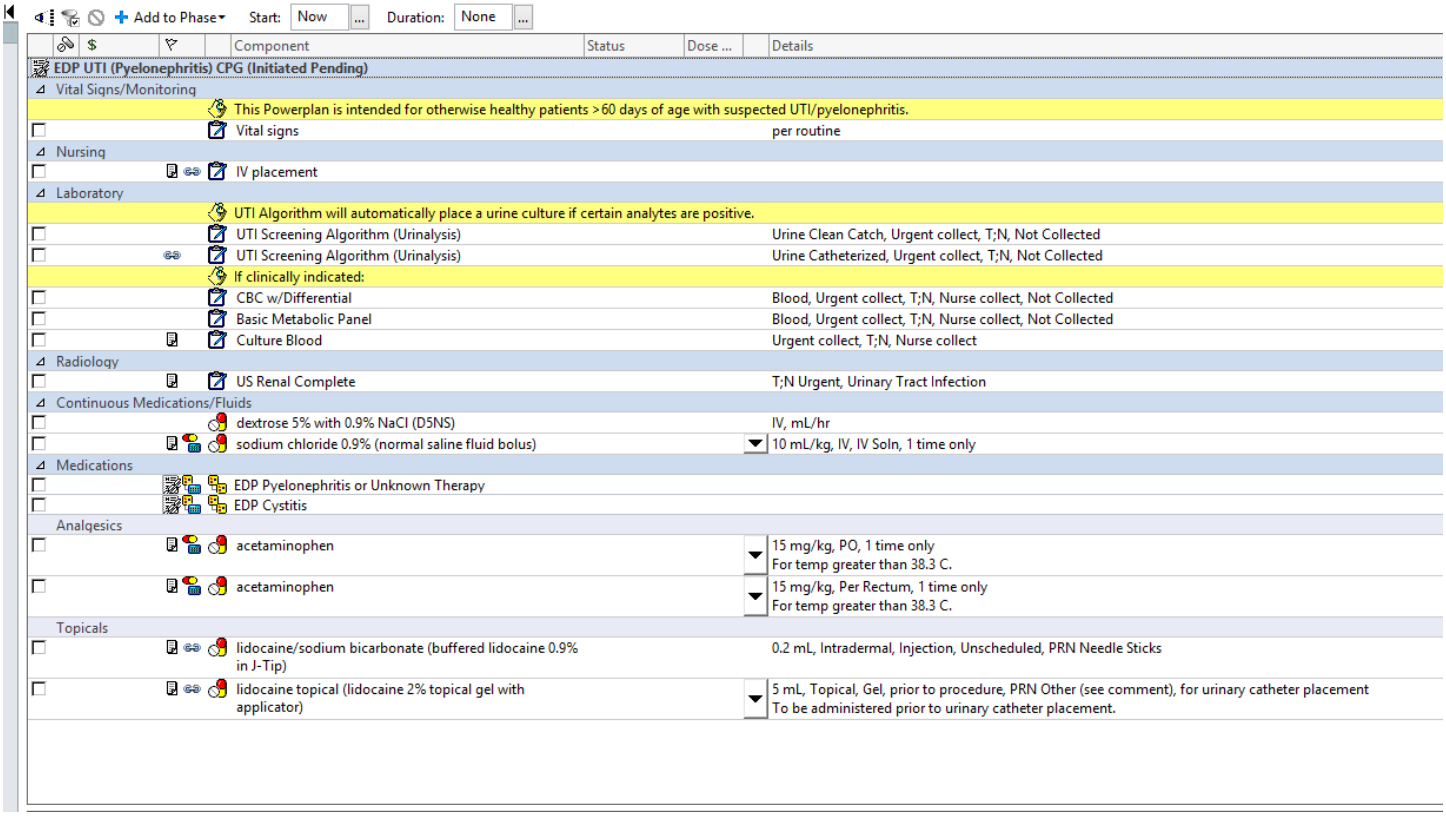
Reference Standard

Target condition and reference standard(s)	Urine Culture • A specimen was considered positive for UTI if a single organism (pure colonies) was cultured at a concentration of $\geq 10^5$ CFU/ml. • In instances of mixed bacterial growth, the procedure was repeated with fresh samples of patients. These were done to rule out possible contamination.
A. Risk of Bias	
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear concern

Flow and Timing

A. Risk of Bias		
Target condition and reference standard(s)	• Unclear if tests are done at the same time	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk
Notes	• Patients were asked to provide a clean catch midstream urine in a sterile screw capped universal container	

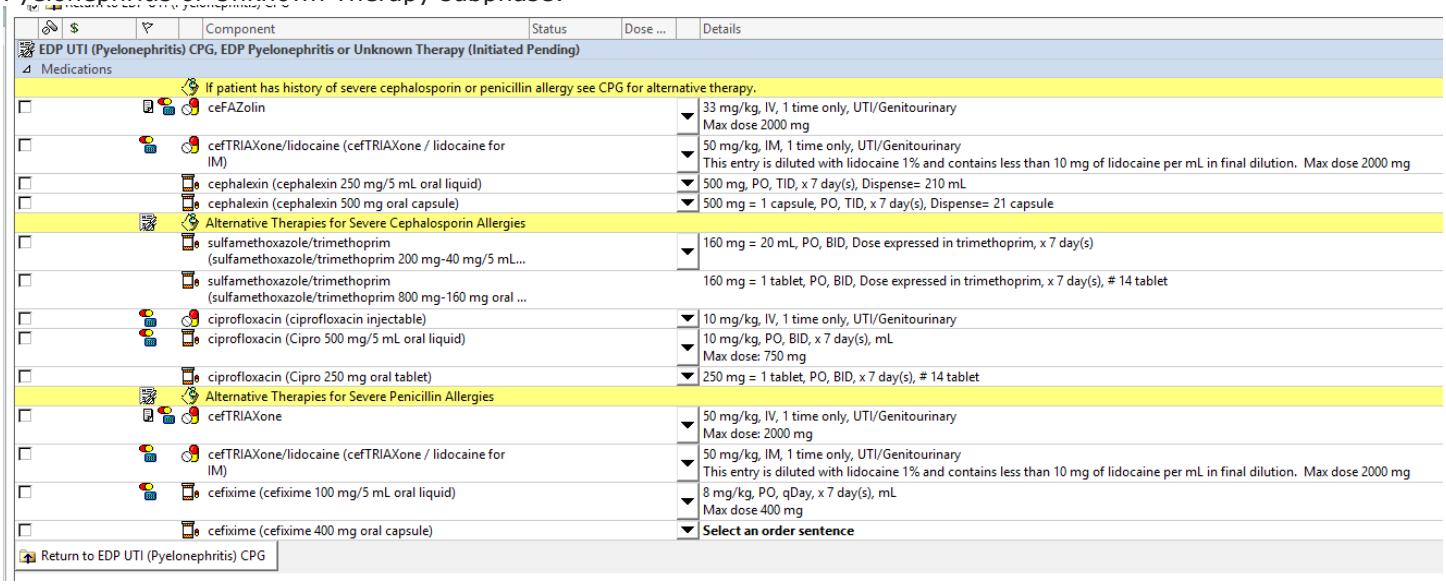
Appendix B: Emergency Department/Urgent Care Powerplan



Add to Phase | Start: Now | Duration: None

Component	Status	Dose ...	Details
EDP UTI (Pyelonephritis) CPG (Initiated Pending)			
Vital Signs/Monitoring			
This Powerplan is intended for otherwise healthy patients >60 days of age with suspected UTI/pyelonephritis.			
Vital signs			per routine
Nursing			
IV placement			
Laboratory			
UTI Algorithm will automatically place a urine culture if certain analytes are positive.			
UTI Screening Algorithm (Urinalysis)			Urine Clean Catch, Urgent collect, T;N, Not Collected
UTI Screening Algorithm (Urinalysis)			Urine Catheterized, Urgent collect, T;N, Not Collected
If clinically indicated:			
CBC w/Differential			Blood, Urgent collect, T;N, Nurse collect, Not Collected
Basic Metabolic Panel			Blood, Urgent collect, T;N, Nurse collect, Not Collected
Culture Blood			Urgent collect, T;N, Nurse collect
Radiology			
US Renal Complete			T;N Urgent, Urinary Tract Infection
Continuous Medications/Fluids			
dextrose 5% with 0.9% NaCl (D5NS)			IV, mL/hr
sodium chloride 0.9% (normal saline fluid bolus)			10 mL/kg, IV, IV Soln, 1 time only
Medications			
EDP Pyelonephritis or Unknown Therapy			
EDP Cystitis			
Analgesics			
acetaminophen			15 mg/kg, PO, 1 time only For temp greater than 38.3 C.
acetaminophen			15 mg/kg, Per Rectum, 1 time only For temp greater than 38.3 C.
Topicals			
lidocaine/sodium bicarbonate (buffered lidocaine 0.9% in J-Tip)			0.2 mL, Intradermal, Injection, Unscheduled, PRN Needle Sticks
lidocaine topical (lidocaine 2% topical gel with applicator)			5 mL, Topical, Gel, prior to procedure, PRN Other (see comment), for urinary catheter placement To be administered prior to urinary catheter placement.

Pyelonephritis or Unknown Therapy subphase:



Component	Status	Dose ...	Details
EDP UTI (Pyelonephritis) CPG, EDP Pyelonephritis or Unknown Therapy (Initiated Pending)			
Medications			
If patient has history of severe cephalosporin or penicillin allergy see CPG for alternative therapy.			
ceFAZolin			33 mg/kg, IV, 1 time only, UTI/Genitourinary Max dose 2000 mg
cefTRIAXone/lidocaine (cefTRIAXone / lidocaine for IM)			50 mg/kg, IM, 1 time only, UTI/Genitourinary This entry is diluted with lidocaine 1% and contains less than 10 mg of lidocaine per mL in final dilution. Max dose 2000 mg
cephalexin (cephalexin 250 mg/5 mL oral liquid)			500 mg, PO, TID, x 7 day(s), Dispense= 210 mL
cephalexin (cephalexin 500 mg oral capsule)			500 mg = 1 capsule, PO, TID, x 7 day(s), Dispense= 21 capsule
Alternative Therapies for Severe Cephalosporin Allergies			
sulfamethoxazole/trimethoprim (sulfamethoxazole/trimethoprim 200 mg-40 mg/5 mL...			160 mg = 20 mL, PO, BID, Dose expressed in trimethoprim, x 7 day(s)
sulfamethoxazole/trimethoprim (sulfamethoxazole/trimethoprim 800 mg-160 mg oral ...			160 mg = 1 tablet, PO, BID, Dose expressed in trimethoprim, x 7 day(s), # 14 tablet
ciprofloxacin (ciprofloxacin injectable)			10 mg/kg, IV, 1 time only, UTI/Genitourinary
ciprofloxacin (Cipro 500 mg/5 mL oral liquid)			10 mg/kg, PO, BID, x 7 day(s), mL Max dose: 750 mg
ciprofloxacin (Cipro 250 mg oral tablet)			250 mg = 1 tablet, PO, BID, x 7 day(s), # 14 tablet
Alternative Therapies for Severe Penicillin Allergies			
cefTRIAXone			50 mg/kg, IV, 1 time only, UTI/Genitourinary Max dose: 2000 mg
cefTRIAXone/lidocaine (cefTRIAXone / lidocaine for IM)			50 mg/kg, IM, 1 time only, UTI/Genitourinary This entry is diluted with lidocaine 1% and contains less than 10 mg of lidocaine per mL in final dilution. Max dose 2000 mg
cefixime (cefixime 100 mg/5 mL oral liquid)			8 mg/kg, PO, qDay, x 7 day(s), mL Max dose 400 mg
cefixime (cefixime 400 mg oral capsule)			**Select an order sentence**
Return to EDP UTI (Pyelonephritis) CPG			

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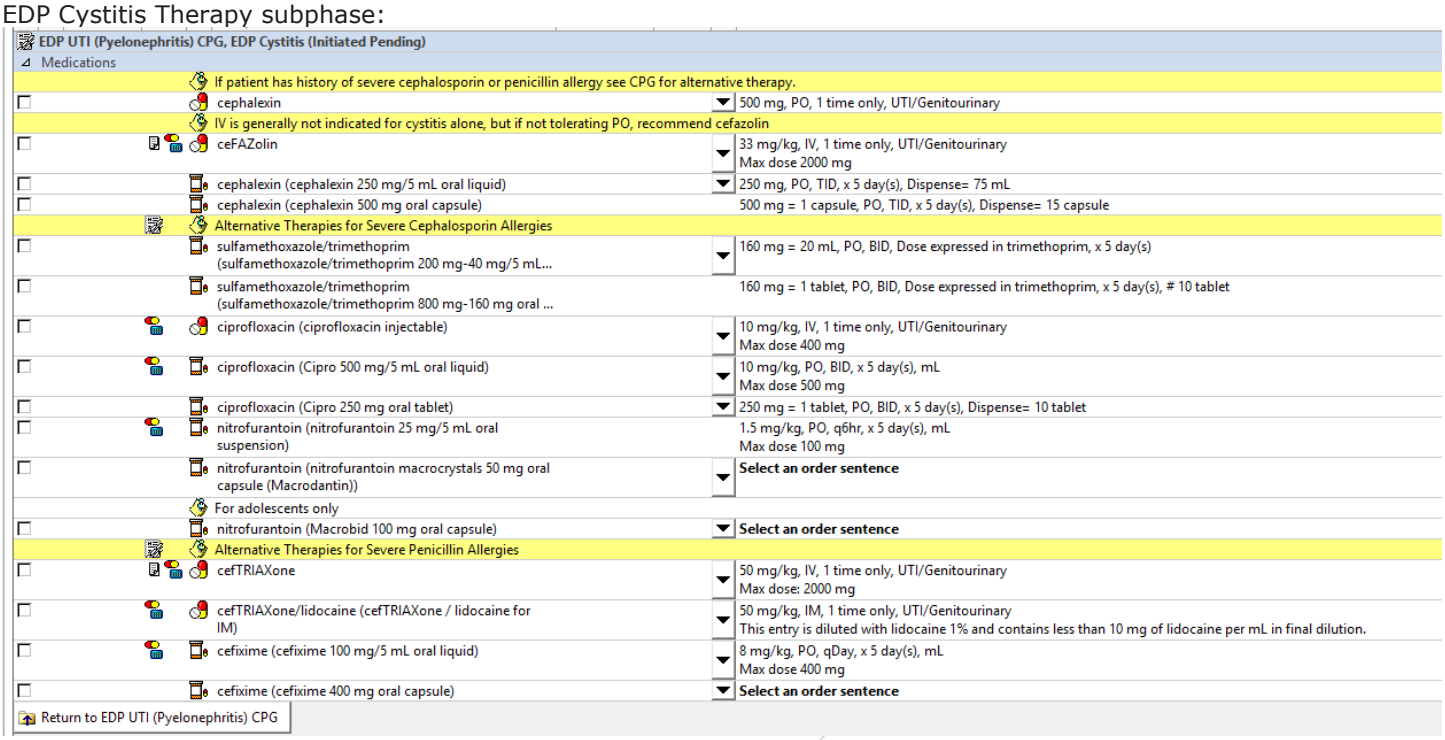
EDP Cystitis Therapy subphase:



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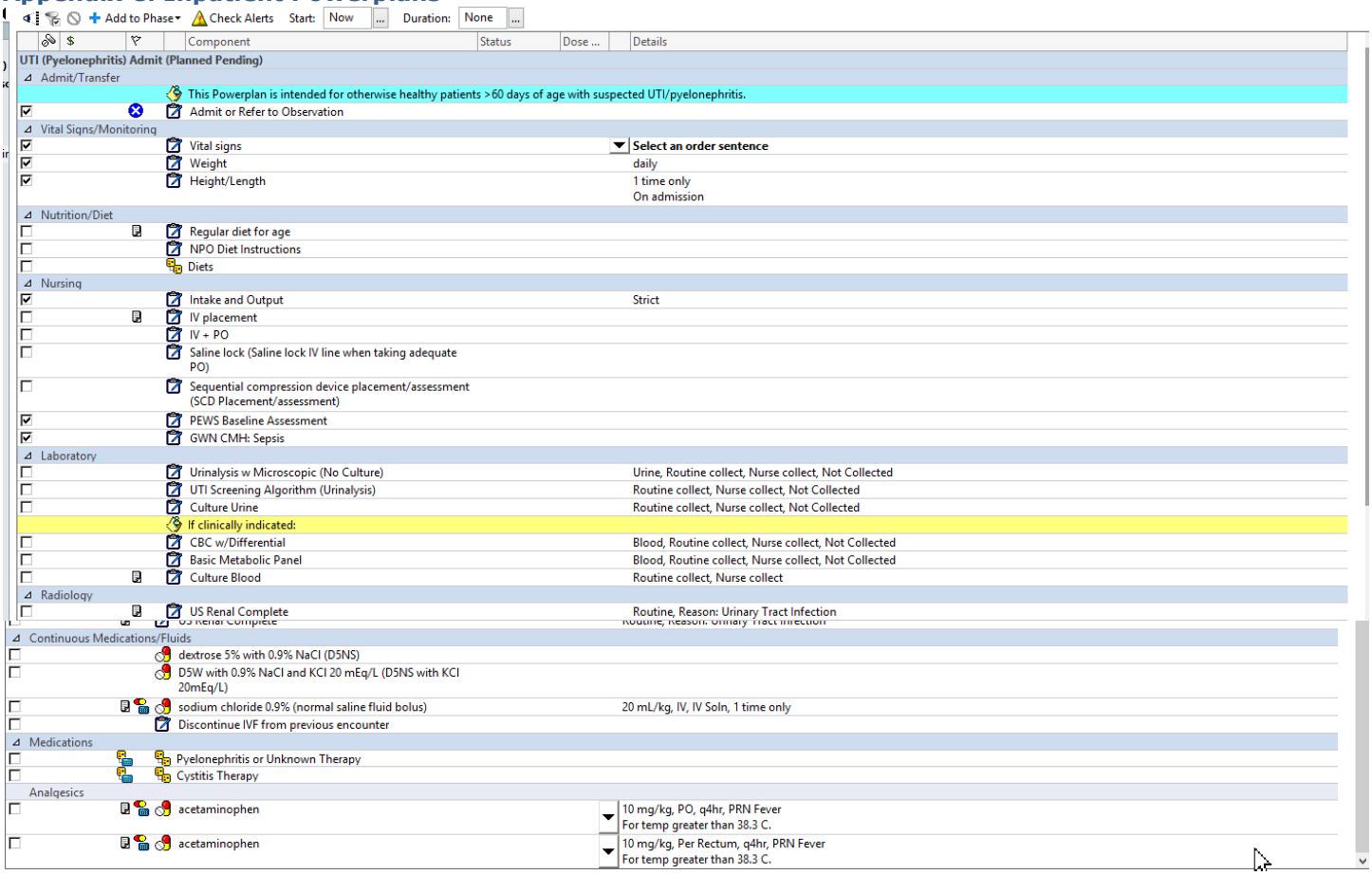
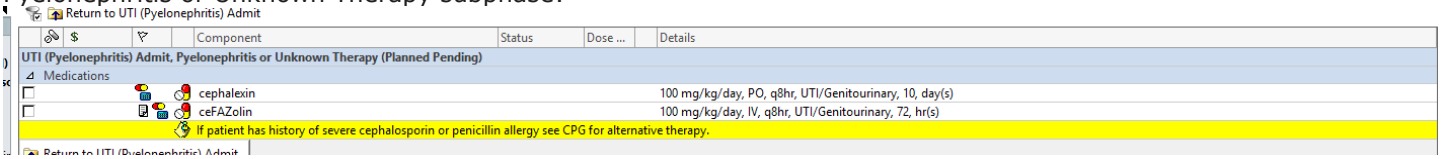
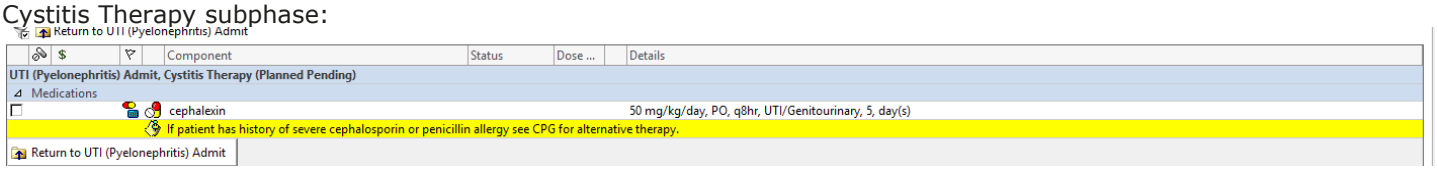
Appendix C: Inpatient Powerplans



Pyelonephritis or Unknown Therapy subphase:



Cystitis Therapy subphase:



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Appendix D: AGREE II Assessment for Children's Mercy Hospitals' UTI CPG

*AGREE II[a] Summary for this Clinical Practice Guideline**

Domain	Percent Agreement
Scope and purpose	92%
Stakeholder involvement	69%
Rigor of development	84%
Clarity and presentation	89%
Applicability	96%
Editorial independence	96%
Reviewer's recommendation for guideline use	Yes

**Note:* This assessment reflects the views obtained from one external clinician and one internal clinician.

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