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Consensus Statement | Infectious Diseases

Guidelines for the Prevention, Diagnosis, and Management of Urinary Tract Infections in Pediatrics and Adults

A WikiGuidelines Group Consensus Statement

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Abstract

IMPORTANCE Traditional approaches to practice guidelines frequently result in dissociation between strength of recommendation and quality of evidence.

OBJECTIVE To create a clinical guideline for the diagnosis and management of urinary tract infections that addresses the gap between the evidence and recommendation strength.

EVIDENCE REVIEW This consensus statement and systematic review applied an approach previously established by the WikiGuidelines Group to construct collaborative clinical guidelines. In May 2023, new and existing members were solicited for questions on urinary tract infection prevention, diagnosis, and management. For each topic, literature searches were conducted up until early 2024 in any language. Evidence was reported according to the WikiGuidelines charter: clear recommendations were established only when reproducible, prospective, controlled studies provided hypothesis-confirming evidence. In the absence of such data, clinical reviews were developed discussing the available literature and associated risks and benefits of various approaches.

FINDINGS A total of 54 members representing 12 countries reviewed 914 articles and submitted information relevant to 5 sections: prophylaxis and prevention (7 questions), diagnosis and diagnostic stewardship (7 questions), empirical treatment (3 questions), definitive treatment and antimicrobial stewardship (10 questions), and special populations and genitourinary syndromes (10 questions). Of 37 unique questions, a clear recommendation could be provided for 6 questions. In 3 of the remaining questions, a clear recommendation could only be provided for certain aspects of the question. Clinical reviews were generated for the remaining questions and aspects of questions not meeting criteria for a clear recommendation.

CONCLUSIONS AND RELEVANCE In this consensus statement that applied the WikiGuidelines method for clinical guideline development, the majority of topics relating to prevention, diagnosis, and treatment of urinary tract infections lack high-quality prospective data and clear recommendations could not be made. Randomized clinical trials are underway to address some of these gaps; however further research is of utmost importance to inform true evidence-based, rather than eminence-based practice.

+ Supplemental content

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Introduction

Urinary tract infections (UTIs) are among the most common infections globally, notably impacting patient quality of life and posing substantial clinical and economic challenges. UTIs exhibit diverse etiologies and clinical severities, from simple cystitis to pyelonephritis and life-threatening sepsis. Diagnosis can be a challenge, due to the lack of validated, highly accurate testing. Management is further complicated by evolving multidrug resistance. Despite advancements in diagnosis and treatment, UTIs can cause high morbidity and mortality, with profound implications in both community and health care settings.

In this third WikiGuidelines consensus statement, we provide an evidence-based approach to UTI management developed by a global network of experts for practical use across diverse clinical settings. This guideline fills a critical gap by providing pragmatic, broadly applicable recommendations tailored for generalist care and systems-based practice. Our guidance is rooted in the best available evidence and is designed for clinicians from various backgrounds and health care environments. It emphasizes a patient-centered approach to the diagnosis, prevention and treatment of UTIs and related genitourinary infections.

Methods

Our multinational team includes 54 experts from 12 countries, including 31 physicians and 23 pharmacists or PhDs with expertise in internal medicine, pediatrics, infectious diseases, and/or microbiology (eTable 1 and 2 in the Supplement). This study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline and followed the WikiGuidelines charter, which requires issuing clear recommendations only when supported by sufficient hypothesis-confirming evidence, including 2 well-conducted concordant randomized clinical trials (RCTs) or 1 well-conducted RCT and a well-conducted concordant prospective observational study. When evidence does not meet these criteria, a review of the literature and discussion is presented in lieu of a recommendation with the goal of proposing reasonable management strategies that maximize benefits, minimize harms, and avoid definitive recommendations for unsubstantiated practices.

On March 15, 2023, crowdsourcing efforts began via social media to identify experts interested in contributing to the guideline development. Authors were selected based on their active professional licenses and relevant clinical expertise, with additional participants chosen for their technical expertise, such as medical librarianship, epidemiology, and biostatistics. The steering committee, elected by the board of directors, selected the chair and cochair to oversee the development of the guideline. On May 1, 2023, we solicited questions from authors about UTI prevention, diagnosis, and management, and organized by theme. Specialized groups were formed, and section leads were appointed by the cochairs to address the 5 distinct themes. Volunteer authors and section leads produced each section through performing extensive literature reviews in PubMed, Medline, and other databases without date or language restrictions. Initial drafts created by the groups were reviewed and refined by the primary and senior authors, followed by collaborative review and feedback from the entire group. Consensus was achieved through a structured process involving a series of meetings, literature reviews, and iterative revisions, with the final approval requiring either a consensus or, if necessary, a majority vote among the committee members. After multiple rounds of revisions and feedback, a finalized version for each section was realized and compiled into a cohesive manuscript by the primary and senior authors.

Results

Section 1: Prophylaxis and Prevention

An overview of findings relating to empirical treatment can be found in **Table 1**. Additional information can be found in eAppendix 1 in the Supplement.

Question 1: What Is the Role of Pharmacotherapy for the Prevention of UTIs?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Pharmacotherapy can be considered for the prevention of UTIs in women with recurrent UTIs (Table 1). Postcoital administration of trimethoprim/sulfamethoxazole (TMP/SMX) or ciprofloxacin appears to reduce the incidence of UTIs in women compared with placebo.[1] No significant difference in effectiveness between intermittent, defined as the use of antibiotics after a trigger such as coitus, and continuous strategies has been demonstrated in high quality studies.[2] Benefits of antibiotic prophylaxis appear confined to their usage period and the optimal duration that balances individual and ecological risks with effectiveness are unclear. Observational data indicate that nitrofurantoin, norfloxacin, and TMP/SMX are comparatively effective; however, conclusions are limited based on the study design.[3] There is limited and conflicting data on antibiotic prophylaxis for children.[4-6]

Question 2: Is There a Role for Cranberry Juice or Supplements in the Prevention of UTIs?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for the role of cranberry juice or supplements in the prevention of UTIs. Most prospective studies have indicated that cranberry products can reduce the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, children, and individuals susceptible to UTIs after interventions (Table 1).[7-23] Evidence for their use in older adults, those with bladder emptying problems, or pregnant women is insufficient to make a clear recommendation for or against use.

Question 3: Can Water Intake Play a Role in the Prevention of UTIs?

The clinical review found insufficient quality of evidence to enable a clear recommendation. One RCT[24] that explored the effect of hydration on UTIs found that increased water intake significantly reduced cystitis frequency in healthy women. This RCT included 140 healthy women with recurrent cystitis, defined as 3 or more episodes in the past year, who drank less than 1.5 L of fluid per day.

Table 1. Strategies to Prevent UTIs

Strategy	Level of evidence	Intervention	Comments
Continuous or postcoital antimicrobial prophylaxis	Clinical review	TMP/SMX: continuous, 40 mg/200 mg once daily or 40 mg/200 mg 3 times weekly; postcoital, 40 mg/200 mg or 80 mg/200 mg once postcoitus; Nitrofurantoin: continuous, 50 mg or 100 mg daily; postcoital, 50 mg or 100 mg once postcoitus	The decision to use antibiotic prophylaxis must balance the need for prevention against the risk of adverse drug events, antimicrobial resistance, and microbiome disruption.[a]
Cranberry products	Clear recommendation	Cranberry products containing proanthocyanidin levels of 36 mg	Cranberry products can reduce the recurrent UTIs in women, children, and individuals susceptible to UTIs. Data for older people, those with bladder emptying problems, or pregnant women is insufficient.
Probiotics	Clinical review	No recommendation	Studies were heterogenous with regard to patient populations, specific probiotics, route of administration, and study design.
Vaginal estrogen	Clear recommendation	Vaginal estrogen, such as vaginal rings, vaginal insert or vaginal cream	There is a wide variety of formulations and local delivery methods. Availability may vary in different countries or geographic regions.
Increased water intake	Clinical review	Additional 1.5L of water	Water intake was shown to decrease UTIs in 1 RCT among healthy women. Given the low-risk nature of the intervention, pending a confirmatory study, it is reasonable to offer this intervention to healthy women with recurrent UTIs.
Methenamine hippurate	Clear recommendation	Methenamine hippurate: 1 g twice daily; methenamine mandelate: 1 g every 6 hours	Methenamine is an appealing antimicrobial-sparing intervention to reduce UTIs in patients without incontinence and a fully functional bladder.

Abbreviations: RCT, randomized clinical trial; TMP/SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection.

[a] Consider use of other options reviewed in eAppendix 1 of the Supplement in more detail prior to continuous or postcoital antimicrobials.

Participants were randomly assigned to either drink an additional 1.5 L of water daily or no additional fluids for 12 months. An observational nursing home study[25] was unable to demonstrate a benefit; however, it was underpowered. Beyond this single RCT,[24] studies are limited and further research is needed to confirm these findings and explore this intervention in broader populations (Table 1).

Question 4: Is There a Role for Topical Estrogen in the Prevention of UTIs?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for the use of topical estrogen to prevent UTIs. Based on available evidence from 30 RCTs and 1 large retrospective observational study, topical estrogen is effective at reducing recurrent UTIs in postmenopausal women (Table 1).[26] The loss of estrogen during perimenopause causes changes within the vaginal microbiome, which can lead to a loss of *Lactobacillus* species, an increase in vaginal pH, and an increased risk of UTIs.[27] The use of topical estrogen may help to reduce vaginal atrophy, restore the vaginal microbiome, and reduce the frequency of UTIs.[28] Recent evidence supports using vaginal estrogen therapy for breast cancer patients with genitourinary symptoms when nonhormonal treatments fail.[29] Topical estrogen is thought to have minimal systemic absorption and no concerning safety signals with regard to the risk of stroke, venous thromboembolism, invasive breast cancer, colorectal cancer, or endometrial cancer were identified in a large prospective cohort study of more than 45 000 women.[30] It remains reasonable for biological females with a history of estrogen-related malignant neoplasms to discuss the risk and benefit of this treatment with their health care team prior to initiation.

Question 5: Is There a Role for Methenamine Hippurate in the Prevention of UTIs?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for the use of methenamine hippurate to prevent UTIs. Methenamine, which was approved in 1967 for recurrent UTI prophylaxis in those aged 12 years and older, works by releasing formaldehyde in acidic urine, thus resulting in bacteriostasis. A systematic review,[31] which included a multicenter, open-label, randomized noninferiority trial conducted in the UK from June 2016 to June 2018, compared the efficacy of methenamine with daily low-dose antibiotics in preventing recurrent UTIs in women aged 18 years and older and found that methenamine was noninferior to antibiotics for the prevention of UTIs. Similarly, a nonblinded RCT compared methenamine with trimethoprim for preventing recurrent UTIs over 12 months in women aged 18 years and older found noninferiority for methenamine, with no significant difference in UTI recurrence rates between the 2 groups and similar adverse effects.[32] Therefore, we recommend the use of methenamine as an alternative to prophylactic antibiotics in patients with intact bladder anatomy (Table 1).

Question 6: Are Probiotics Effective in the Prevention of UTIs?

The clinical review found insufficient quality of evidence to enable a clear recommendation. There is inconclusive evidence to recommend for or against the use of oral or vaginal probiotics to prevent UTIs (Table 1). Studies were heterogeneous as it pertains to the patient populations (children, premenopausal women, postmenopausal women, complicated UTI in patients with comorbidities), specific probiotics, route of administration, and study design.[33-36]

Question 7: Is There a Role for *D*-Mannose in the Prevention of UTIs?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Despite biological plausibility for effectiveness,[37] there is currently insufficient evidence to support or refute the use of *D*-mannose for the prevention of UTIs. Only 3 RCTs,[38-40] 1 small open-label prospective cohort study,[41] and a subgroup of another prospective cohort study[42] evaluated *D*-mannose alone for only prevention (not treatment) of UTIs. Discordant or uncertain results among the prospective studies along with small sample sizes and heterogeneity of specific *D*-mannose regimens, study populations, comparators, UTI definitions, potential for reporting bias, and follow-up periods preclude a clear recommendation for or against its use. Although poorly reported, adverse effects

were seemingly infrequent, and most included gastrointestinal symptoms and vaginal burning.[40,43,44]

Section 2: Diagnosis and Diagnostic Stewardship

An overview of findings relating to diagnosis and diagnostic stewardship can be found in **Table 2**. Additional information can be found in eAppendix 2 in the Supplement.

Question 8: What Are the Clinical Definitions of Cystitis, Complicated UTIs, and Pyelonephritis?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Cystitis and pyelonephritis are typically diagnosed clinically through signs and symptoms with evidence of inflammation (pyuria) and the presence of pathogenic bacteria in the urine (Table 2). Typical nomenclature includes the use of terms, such as cystitis, uncomplicated UTI, complicated UTI, and pyelonephritis. Cystitis, an inflammation of the bladder often indicated by dysuria, urgency, and suprapubic pain, is typically described not to show systemic infection signs like fever. Unfortunately, complicated UTI lacks a standard clinical definition due to diverse criteria in literature and guidelines. Complicated UTIs may involve catheters or other foreign bodies, complicating factors like structural anomalies or immunosuppression, or systemic symptoms. Pyelonephritis, kidney inflammation due to infection, includes cystitis symptoms plus systemic signs like fever and flank pain. More precise clinical definitions, based on clinical studies linked to outcomes, are needed. Most WikiGuidelines authors strongly encourage the use of more precise descriptions of UTI in clinical practice rather than continuing to use vague terms, such as complicated or uncomplicated.

Question 9: What Is the Role and the Sensitivity and Specificity of a Urinalysis (UA) for the Diagnosis of UTIs and When Should Clinicians Order Urine Cultures?

The clinical review found insufficient quality of evidence to enable a clear recommendation. A UA encompasses physical, chemical, and microscopic evaluations designed to aid in diagnosing kidney, metabolic, oncologic, and infectious disorders. Unfortunately, the diagnostic value of UA for UTI is limited.[45,46] While the absence of pyuria can help rule out infection in most patient populations, the positive predictive value of pyuria for diagnosing infection is exceedingly low as it often indicates the presence of genitourinary inflammation due to many other possible noninfectious reasons (**Table 3**). For these reasons, WikiGuidelines authors believe that evidence-based diagnosis of UTI should be primarily based on clinical symptoms. Clinical symptoms may be integrated with UA findings, but authors caution clinicians to not rely solely on the UA alone. Urine cultures are reasonable for complicated cases and/or recurrent UTIs, particularly in suspected pyelonephritis, to

Table 2. Clinical Practice Guideline Definitions of UTI Syndromes in Adults[a]

Defining term(s)	Proposed IDSA	Current IDSA	EAU	AUA, CUA, and SUFU
Complicated UTI and acute pyelonephritis	Any infection beyond the bladder, includes pyelonephritis, CAUTI, febrile or bacteremic patients	Urinary symptoms plus functional or structural abnormalities of the urinary tract. CVA pain and tenderness, often with fever (pyelonephritis)	Dysuria, urgency, frequency, flank pain, CVA tenderness, suprapubic pain, fever, chills, nausea, vomiting; anatomical or functional abnormalities of the urinary tract (eg, obstruction, incomplete voiding due to detrusor muscle dysfunction; presence of diabetes or immunosuppression	Anatomical or functional abnormality of the urinary tract (eg, stone disease, diverticulum, neurogenic bladder); immunocompromised host; multidrug resistant bacteria
Uncomplicated UTI	All other infections not defined as complicated	Frequency, urgency, dysuria, or suprapubic pain in a woman with a normal genitourinary tract	Dysuria, frequency and urgency and the absence of vaginal discharge; limited to nonpregnant women with no known relevant anatomical and functional abnormalities or comorbidities	Dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, or new or worsening incontinence; female host; no known factors that would increase susceptibility to develop UTI

Abbreviations: AUA, American Urological Association; CAUTI, catheter-associated urinary tract infection; CUA, Canadian Urological Association; CVA, costovertebral angle; EAU, European Association of Urology; IDSA, Infectious Disease Society of America; SUFU, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; UTI, urinary tract infection.

[a] See eAppendix 2 of the Supplement for detailed supporting information.

guide targeted therapy. In simple uncomplicated cystitis in healthy nonpregnant patients, routine cultures are not necessary.[47,48]

Question 10: What Is the Role of UA and Urine Culture Testing for the Workup of Fever?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Routine use of UA and urine cultures for the workup of fever in hospitalized patients leads to unnecessary testing and antimicrobial use.[46,49,50] Studies show that UTIs, including catheter-associated UTIs (CAUTI), are infrequently the source of fever, particularly in the absence of urinary tract obstruction, recent urological procedures, or immunocompromise.[51] Consequently, urine testing should not be automatic in febrile patients, especially geriatric patients, or those with known nonurinary sources of fever and should be reserved for cases with specific urinary or related symptoms. Further research is needed to establish clear criteria for urine testing in febrile patients.

Question 11: How Can Diagnostic Stewardship Strategies Be Effectively Implemented in the Management of UTIs to Prevent Unnecessary Treatment of Asymptomatic Bacteriuria?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Effective management of UTI hinges on appropriate diagnostic testing and antimicrobial stewardship, aiming to prevent the misuse of antibiotics for ASB. Symptom-based testing is key to ensure appropriate urine culture testing and proper diagnosis of UTI.[52,53] A 2017 systematic review[54] showed 45% of included patients experienced inappropriate initiation of antimicrobial treatment for ASB; various interventions, such as education on diagnostic protocols, provided a significant absolute risk reduction of 33%. Avoiding overtesting and resulting overtreatment of ASB is essential to preserving antimicrobial effectiveness.

Question 12: What Is the Role of Novel Molecular Tests in the Diagnosis of UTI?

The clinical review found insufficient quality of evidence to enable a clear recommendation. The role of molecular techniques for UTI diagnosis is currently limited. Molecular diagnostics cannot distinguish true infection from ASB. Urine culture is the current reference standard for confirming the etiologic pathogen in patients with suspected infection. Although 100 000 colony forming unit (CFU)/mL has been considered the historical standard threshold for bacteriuria and diagnosing UTIs, lower CFU counts can still indicate significant infections in symptomatic patients.[55-58] In contrast, molecular techniques are generally unable to determine bacterial viability or quantitation in urine

Table 3. Diagnostic Testing Performance for Urinary Tract Infections[a]

Test results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Dipstick				
Positive leukocyte esterase	72-97	41-86	43-56	82-91
Positive nitrite	19-48	92-100	50-83	70-88
Positive leukocyte esterase or nitrite	46-100	42-98	52-68	78-98
Microscopy, WBC/μL				
>5[b]	90-96	47-50	56-59	83-95
10	100	36	NA	NA
50	98	66	NA	NA
100	93	71	NA	NA
200	89	86	NA	NA
300	84	88	NA	NA
400	77	92	NA	NA
Imaging				
Ultrasonography	74.3	56.7	NA	NA
Computerized tomography	81-84	87.5	NA	NA
Magnetic resonance imaging	100	81.8	NA	NA

Abbreviations: HPF, high power field; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value; WBC, white blood cell.

[a] See Section 2 of the Supplement for detailed supporting information.

[b] WBC/HPF.

specimens.[59] These factors are crucial to differentiate colonization vs infection and to delineate pathogenic organisms vs commensal flora. The increased sensitivity of these molecular tests may lead to overtreatment by detecting clinically insignificant bacteria, especially now that metagenomics has identified endogenous genitourinary microflora,[60-64] underscoring the need for clear guidelines to avoid unnecessary therapy. More research is required to determine the ideal role of molecular testing in UTI diagnosis.

Question 13: What Is the Role of Different Imaging Modalities, Such as Ultrasonography and Computed Tomography, for the Diagnosis of UTIs, and What Is the Sensitivity and Specificity These Imaging Modalities?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Computed tomography (CT) scans do not appear to be useful in the routine initial diagnostic workup of cystitis or pyelonephritis and may not routinely alter treatment[65,66] CT imaging may be useful if symptoms persist or worsen beyond 72 hours or if there are concerns for kidney calculi, kidney abscess, or an alternative focus of infection.[67-69] Contrast CT imaging is best discussed with the radiologist but may have advantages in terms of detecting kidney abscesses. Ultrasonography, while safer and more accessible, has limited accuracy but may be a preferrable first imaging modality in younger patients, pregnancy, and/or kidney transplant recipients because there is no associated ionizing radiation, and may be able to more directly visualize the transplanted organ(s) (**Table 4**). Magnetic resonance with or without contrast and/or diffusion-weighted imaging is less effective for early disease detection and stone visualization but may also have an advantage in identifying graft infection (Table 4).[70,71] We caution clinicians to only obtain radiographic studies if they are likely to alter management for a patient with known or suspected UTI.

Question 14: What Are the Limitations of Usual Diagnostics in Patients With Indwelling Urinary Catheters or Ileal Conduits?

The clinical review found insufficient quality of evidence to enable a clear recommendation. UA has a very low specificity in diagnosing UTIs in patients with indwelling urinary catheters or ileal conduits but has excellent negative predictive value.[72] This suggests that a negative UA can rule out CAUTI for patients with functioning bone marrow, but given the low specificity of UA in patients with urinary catheters or ileal conduits, a positive UA does not mean the patient has a CAUTI. In addition, urine cultures are not reliable tests for patients with chronic urinary catheters or ileal conduits.[73-75] In these cases, bacteriuria is almost always present regardless of symptoms and are a likely source of appropriate initiation of antimicrobial treatment.

Section 3: Empirical Treatment

An overview of findings relating to empirical treatment can be found in Table 3. Additional information can be found in eAppendix 3 in the Supplement.

Question 15: What Are Reasonable Empirical Treatment Regimen(s) for Pediatric or Adult Patients Diagnosed With a UTI?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for empirical treatment regimens for pediatric and adult patients diagnosed with UTIs. Empirical treatment regimens for pediatric and adult patients should contain antimicrobials that have historically demonstrated efficacy and safety in the treatment of UTIs, achieve adequate urinary concentrations, and provide reliable activity against the most common pathogens based on local resistance rates. A proposed framework for selecting empirical treatment regimens is presented in eFigure 1 and eFigure 2 in the Supplement. Presence of risk factors for antimicrobial resistance along with clinical severity also play an important role in the selection of empirical choices.[76,77,182] For patients with uncomplicated cystitis, nitrofurantoin is a reasonable drug of choice, based on robust evidence of efficacy and its ability to spare use of more systemically active agents for treating other

Table 4. Duration of Treatment Based on Syndrome and Antimicrobial Class Used

Syndrome and antimicrobial class	Duration of therapy (level of evidence)	Comments
Adult cystitis[a]		
Aminoglycosides	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Multiple observational studies suggest a single dose of an aminoglycoside achieve high clinical and/or microbiological cure rates; no comparative literature exists
β-lactams	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Optimal duration may depend on the specific agent and dosing used. Heterogeneity in study design and β-lactam agent and dose used in studies precludes a clear recommendation
Fluoroquinolones	3 d (clear recommendation)	Due to risk of individual and ecological collateral damage, should not be used if other treatment options exist.
Fosfomycin (oral)	Single dose (clear recommendation)	Alternative dosing strategies have only been studied in RCTs and observational studies of febrile UTI, bacteremic UTI, and pyelonephritis
Nitrofurantoin	5 d (clear recommendation)	5-d and 7-d Courses result in comparable clinical outcomes; may use with CrCl as low as 30 mL/min
Pivmecillinam	3 d (clear recommendation)	3 d Regimens appear to have comparable efficacy as longer regimens and various regimens of comparators commonly used in contemporary practice.
TMP/SMX	3 d (clear recommendation)	Contemporary *Escherichia coli* resistance rates in most geographical regions limit utility as first-line treatment.
Adult pyelonephritis[b]		
Aminoglycosides	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Multiple observational studies suggest monotherapy may be effective, however the optimal duration is unknown.
β-lactams	7 d (clear recommendation)	Dose optimization is critical based on analogous data supporting β-lactam use in the treatment of gram-negative bloodstream infection and outcomes of RCTs using IV β-lactams. 3 RCTs demonstrate comparable outcomes with 7 d of treatment vs 2-, 3-, and 6- wk regimens.
Fluoroquinolones	5 to 7 d (clear recommendation)	RCTs supporting 5 d of treatment used ofloxacin or levofloxacin; RCTs supporting 7 d of treatment used ciprofloxacin or fleroxacin. Ofloxacin is a second generation fluoroquinolone similar to ciprofloxacin, so may be reasonable to use 5 d of treatment when using ciprofloxacin as well.
Fosfomycin	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	IV fosfomycin available in some countries may be reasonable empirical treatment for pyelonephritis, but there is a lack of strong data supporting the use of oral fosfomycin for the treatment of pyelonephritis.
TMP/SMX	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Historical durations of 14 d were used based on a series of very small RCTs in the 1970s to 1990s; outcomes of patients who received TMP/SMX in more recent RCTs suggest 7 d may be adequate, but further prospective investigation is needed.
Adult febrile UTI[b]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	When considering the available data for pyelonephritis and gram negative bacteremia from a urinary source, it may be reasonable for febrile UTI to be treated in a similar fashion to pyelonephritis.
Catheter-associated UTI[c]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Data are limited to observational studies and small subgroups of RCTs, precluding a clear recommendation. Observational data suggest 5 to 7 d may be as effective as longer durations.
Gram-negative bacteremia from a urinary source[d,e]	7 d (clear recommendation)	Heterogeneity in trial design and selection and dosing of antimicrobials used limits ability to recommend specific antimicrobial classes. Fluoroquinolones, TMP/SMX, and β-lactams were included in published RCTs demonstrating noninferiority of 7 d to 14 d.
Prostatitis[f]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment for either ABP or CBP.	There is a dearth of data for both acute and chronic bacterial prostatitis that precludes a clear recommendation for duration of treatment in either scenario. Historical durations range from 14 d for ABP to 6 weeks or longer for CBP.

(continued)

Table 4. Duration of Treatment Based on Syndrome and Antimicrobial Class Used (continued)

Syndrome and antimicrobial class	Duration of therapy (level of evidence)	Comments
Pediatric cystitis (>2 mos of age)[g]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Heterogeneity in trial design, inclusion of clinically relevant outcomes precludes a clear recommendation. Numerous RCTs suggest shorter durations are likely effective (3 to 5 d).
Pediatric pyelonephritis (age >2 y)[h]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Quantity and heterogenity of existing data preclude a clear recommendation. Observational data suggest comparably high rates of clinical success when patients are treated for 5 to 9 d compared with longer (10 to 14 d) durations.
Kidney and perinephric abscess[i]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Source control is of utmost importance. Expert opinion does not distinguish between 14 and 21 d of treatment.
Emphysematous cystitis and pyelonephritis[j]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment or emphysematous cystitis or pyelonephritis	May vary widely depending on clinical response and whether percutaneous drainage was performed. When considering the available data for pyelonephritis and Gram-negative bacteremia from a urinary source, it may be reasonable for emphysematous cystitis and pyelonephritis to be treated in a similar fashion to other more clinically severe UTIs, such as febrile UTI, pyelonephritis, and gram negative bacteremia from a urinary source.

Abbreviations: ABP, acute prostatitis; CBP, chronic prostatitis; CrCl, creatinine clearance; IV, intravenous; RCT, randomized clinical trials; TMP/SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection.

[a] See question 21 in eAppendix 4 in the Supplement.

[b] See question 22 in eAppendix 4 in the Supplement.

[c] See question 23 in eAppendix 4 in the Supplement.

[d] See question 24 in eAppendix 4 in the Supplement.

[e] No specific class of antimicrobial can be clearly recommended.

[f] See question 35 in eAppendix 5 in the Supplement.

[g] See question 19 in eAppendix 4 in the Supplement.

[h] See question 20 in eAppendix 4 in the Supplement.

[i] See question 34 in eAppendix 5 in the Supplement.

[j] See question 33 in eAppendix 5 in the Supplement.

infections.[78] For patients with pyelonephritis, TMP/SMX or a first-generation cephalosporin represent reasonable first-line agents but should be dependent upon local resistance rates. Due to low resistance rates and clinical effectiveness, ceftriaxone is the recommended empirical choice for patients who require intravenous therapy, barring any risk factors for multidrug resistance.[79,80] In general, agents with antipseudomonal activity should only be used in patients with risk factors for nosocomial pathogens. However, it may be reasonable to use carbapenem therapy empirically in hemodynamically unstable patients for whom there is a specific concern regarding extended-spectrum β-lactamase-producing bacteria. Overall, selection should be guided by local susceptibilities and patient-specific risk factors.

Question 16: What Are Reasonable Empirical Treatment Regimens for Treatment of a CAUTI?

The clinical review found insufficient quality of evidence to enable a clear recommendation. There is an absence of high-quality data to inform empirical treatment in patients with CAUTI. Observational data suggest that, where possible, it may be preferable to replace or discontinue existing catheters prior to the collection of cultures and initiation of antimicrobial treatment.[81] UTIs diagnosed after catheter exchange are likely to respond similarly to noncatheterized patients. Empirical treatment decisions can be made based on review of the individual patient's urinary tract anatomy or dysfunction, allergies medication list for interactions, microbiological and prior treatment history, the type of UTI (eg, cystitis vs pyelonephritis), and the clinical severity of presentation.

Question 17: What Are the Established Risk Factors for UTI Due to Multidrug Resistant Organisms and When Should Empirical Treatment Account for These Pathogens?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Although no validated models exist, prior health care exposure, previous antibiotic use, and a history of UTI or known colonization seem to be the most consistent and important estimators of development of a UTI due to a multidrug resistant organism (MDRO).[82-84] Due to heterogeneity in the populations and methods of available studies, the timing and/or combination of the exposure(s) and the subsequent effects on the outcome are unclear. There is insufficient data available to clearly guide decisions on when empirical treatment should include the possibility of an MDRO. In the absence of such data, it may be reasonable to suggest that the severity of an infection may be an important driver of empirical antibiotic choice when combined with local resistance patterns, proposed epidemiologic risk factors, and an individualized microbiologic history.

Section 4: Definitive Treatment and Antimicrobial Stewardship

An overview of findings relating to definitive treatment can be found in Table 4. Additional information can be found in eAppendix 4 in the Supplement.

Question 18: What Is Considered Treatment Failure of a UTI and Are There Host-Related Risk Factors That May Influence the Risk of Treatment Failure?

The clinical review found insufficient quality of evidence to enable a clear recommendation. There is no agreed upon universal definition of treatment failure. In general, treatment failure may result from clinical failure, microbiological failure, or a combination thereof. Current US Food and Drug Administration guidance suggests a composite endpoint that includes both clinical and microbiological responses. The true implications of the combination of clinical cure with microbiologic failure at follow-up remains uncertain. An analysis of individual participant data from several phase 3 studies found an increased risk of late clinical failure in patients with clinical cure but microbiological persistence,[85] but this phenomenon is often difficult to distinguish from a new infection. Notably, in 2 recent large RCTs, positive urine cultures at follow-up in patients who had resolved clinical signs and symptoms of infection did not appear to predict a higher risk of relapse of infection within the follow-up period.[86,87] Commonly identified epidemiologic risk factors for treatment failure identified in observational studies include older age, diagnosis of diabetes, presentation with septic shock, pregnancy, and immunosuppression.[88-99] No compelling data exist to support adjusting UTI treatment based on the potential risk factors for treatment failure that have been identified in these retrospective studies.

Question 19: What Is the Appropriate Duration of Treatment of Acute Cystitis in Pediatric Patients Older Than 2 Months of Age?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Based on several randomized trials, shorter courses (3 to 5 days, depending on the antimicrobial used) result in comparable outcomes to longer courses (7 to 14 days) and are reasonable for the treatment of cystitis in children older than 2 months of age when the likelihood of pyelonephritis is deemed to be low.[100-102] Small study size, heterogeneity in trial design (various durations, various antibiotics), end point definitions (with frequent use of positive culture at follow-up defining treatment failure), and outcomes, preclude a clear recommendation for duration of treatment. Several observational studies suggest that a single parenteral dose of an aminoglycoside may be a reasonable alternative treatment option.[103] No data exists to suggest that initial (or any) parenteral treatment for cystitis is necessary in patients who can tolerate oral treatment.

Question 20: What Is the Appropriate Duration of Treatment of Acute Pyelonephritis in Pediatric Patients Older Than 2 Months of Age?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Available randomized trial data are inadequate to provide a clear recommendation on the optimal duration of treatment for acute pyelonephritis in children older than 2 months of age.[86,104,105] Most existing data suggest similarly high rates of clinical success when patients receive 5 to 9 days (depending on the antimicrobial used) when compared with 10 to 14 days total.[106,107]

Question 21: What Is the Appropriate Duration of Treatment for Acute Cystitis in Adults?

Based on the totality of the evidence available, we can provide clear recommendations on the optimal durations of treatment for cystitis (regardless of biological sex) for the antimicrobial classes listed below:

- Nitrofurantoin: 5 days[108-110]
- TMP/SMX: 3 days[109,111,112]
- Fluoroquinolones: 3 days[109,113-118]
- Oral fosfomycin: single dose[78,119-127]
- Pivmecillinam: 3 days[109,128-132]
- Gepotidacin: 5 days[133]

Data are insufficient to enable clear recommendations for duration of treatment for other potential treatment options, including β-lactams and parenteral aminoglycosides. Some pediatric data support a 5-day treatment duration when oral β-lactams are used to treat cystitis.[105]

Question 22: What Is the Appropriate Duration of Treatment for Acute Pyelonephritis and/or Febrile UTI in Adults?

Based on several randomized clinical trials, we can provide a clear recommendation on the duration of therapy for the following antimicrobial classes (regardless of biological sex) for the treatment of acute pyelonephritis:

- Fluoroquinolones: 5 to 7 days[134-139]
- Dose-optimized β-lactams: 7 days[140-143]

The clinical review found insufficient quality of evidence to enable a clear recommendation for fosfomycin, TMP/SMX, and aminoglycoside monotherapy. We cannot provide clear recommendations for pyelonephritis treatment duration with TMP/SMX, fosfomycin, or aminoglycoside monotherapy due to the lack of reproducible high-quality data or heterogeneity across small studies. We are unable to provide a clear recommendation for the treatment duration for febrile UTI. When considering the available data for pyelonephritis and gram-negative bacteremia from a urinary source, it may be reasonable for febrile UTI to be treated in a similar fashion to pyelonephritis.

Question 23: What Is the Appropriate Duration of Treatment for CAUTIs?

The clinical review found insufficient quality of evidence to enable a clear recommendation. The optimal duration of antimicrobial therapy for CAUTIs has not been rigorously evaluated in large RCTs.[81] Data are limited to observational studies or small subgroups of RCTs evaluating complicated UTIs, so a clear recommendation cannot be made. Based on available observational data, 5 to 7 days appears as effective as longer treatment courses and represents a reasonable duration of treatment for most cases of CAUTI in conjunction with catheter exchange and/or removal, if possible.[144] No existing data demonstrate an association between longer courses and improved patient outcomes.

Question 24: What Are Optimal Oral Agents and an Appropriate Duration of Treatment for Gram-Negative Bacteremia From a Urinary Source?

A sufficient quality and quantity of evidence was found to provide a clear recommendation. Multiple RCTs comprised patients with gram negative bacteremia from predominantly urinary sources demonstrate noninferiority of 7 days compared with 14 total days of treatment for a variety of patient-oriented outcomes, such as clinical cure, clinical failure, relapse, and all-cause mortality.[145-148] Thus, we can provide a clear recommendation for 7 days of treatment for gram negative bacteremia from a urinary source when source control has been addressed (if applicable). Whether shorter durations might also be effective is unknown as they have not been studied. These trials tested duration as a strategy and not specific drugs; thus, while no specific class of medications can be recommended, it is also reasonable to ensure that the choice of drug and the doses used are optimized for the patient and a urinary focus of infection.

Question 25: What Are Potential Treatment Option(s) and Appropriate Durations of Treatment for Asymptomatic Bacteriuria in Populations in Which Treatment Is Indicated?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Unnecessary treatment of asymptomatic bacteriuria (ASB) risks side effects without benefit represents low value care and poses a threat to antimicrobial sustainability.[53,149-152] There is no conclusive evidence that there is any population in which treatment of ASB is required and randomized clinical trials are welcomed. There are theoretical reasons and limited evidence which support treatment of ASB in pregnant patients[153,154] and in those undergoing invasive urologic procedures associated with expected mucosal bleeding.[155-158] When treating ASB, the ideal duration of treatment is unknown. In pregnancy, it may be reasonable not to exceed the duration used for symptomatic cystitis (eg, 3 to 5 days, depending on the antimicrobial used). For patients undergoing invasive urologic procedures, most authors believe that many patients could receive a single dose of preoperative prophylaxis prior to the scheduled procedure.

Question 26: What Are Potential Treatment Option(s) and Duration of Treatment for UTIs Caused by Multidrug Resistant Organisms?

The clinical review found insufficient quality of evidence to enable a clear recommendation. The potential treatment option(s) depend on the organism identified and specific resistance mechanisms. To our knowledge, no data exist to suggest that the duration of treatment for UTIs caused by multidrug resistant organisms (MDROs) needs to be modified compared with those caused by nonresistant organisms. We feel it is reasonable to determine a treatment duration based on the anatomical location and clinical severity (eg, cystitis or pyelonephritis) as well as the clinical response to treatment provided that (1) the antimicrobial being used has demonstrated activity against the organism, (2) the antimicrobial has proven or a high likelihood of efficacy for treatment of UTIs, and (3) any applicable source control has been obtained.

Question 27: What Are Effective Antimicrobial Stewardship Strategies That Can Optimize the Rational and Sustainable Use of Antimicrobials in the Setting of Treatment of UTIs?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for deescalation and mostly or all oral treatment. Randomized clinical trials have demonstrated the individual and ecological benefits to antibiotic deescalation and all authors encourage its use when able during the treatment of UTIs.[159,160] Additionally, multiple RCTs demonstrate treatment of a variety of UTIs with all or mostly oral regimens result in comparable outcomes with intravenous-only treatment and may reduce hospital length of stay and adverse events associated with antibiotics and/or central venous catheters.[161-174]

The clinical review found insufficient quality of evidence to enable a clear recommendation for allergy assessment and cascade reporting. Our review did not yield any RCTs evaluating antibiotic allergy assessment specifically for the management of UTIs; however all authors of this consensus statement agree that thorough allergy assessment (and challenge, if indicated) can likely prevent a variety of harms based on existing data and recommendations from specialists in allergy or immunology.[175-177] Although we cannot provide a clear recommendation due to the observational nature of the data, we agree that optimizing the reporting of antimicrobial susceptibility results through selective or cascade reporting is a reasonable strategy to optimize treatment selection.[178-180]

Section 5: Special Populations and Genitourinary Syndromes

An overview of findings relating to special populations can be found in Table 5. Additional information can be found in eAppendix 5 in the Supplement.

Question 28: What Are Special Considerations for the Diagnosis and Treatment of UTI in Older Adults?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Asymptomatic bacteriuria is prevalent in the older adults, particularly in institutionalized individuals, with treatment showing no benefit over placebo.[181,182]Overtesting and overtreatment with antibiotics for these nonsymptomatic cases remains high.[183,184] UTIs are more frequent in the institutionalized older adult populations and clinical tools for assessing symptoms exist to help discourage tests for nondelirium behavioral changes or falls.[183] Using clinical scores alongside microbiological tests is crucial due to the high rates of bacteriuria with pyuria, and the potential misinterpretation of UA results, which often leads to unnecessary antibiotic use.[185,186] Further research comparing clinical prediction scores for UTIs is needed.

Question 29: What Is the Role and Utility of UA and Urine Culture Testing in Pediatric Populations?

The clinical review found insufficient quality of evidence to enable a clear recommendation. In pediatric care, the workup for febrile illness often includes UA and urine culture, particularly in

younger populations where symptoms cannot be elicited.[187] These practices can lead to the overtreatment and overdiagnosis of UTI. Major societies recommend using proper microbiological methods for diagnosis, yet clinical practices deviate, depending on less reliable methods like bagged urine samples.[188-190] The interpretation of UA and colony forming unit counts in urine cultures in the pediatric population are not clearly defined, leading to variability in the diagnosis and treatment of pediatric UTI.

Question 30: For Pediatric Patients, How Do We Delineate Cystitis vs Pyelonephritis When the Child Is Unable to Verbalize Symptoms Characteristic of UTI?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Pediatric cystitis and pyelonephritis are common yet complex conditions in children, impacting quality of life and requiring comprehensive management.[191,192] In pediatric patients, distinguishing cystitis from pyelonephritis can be challenging, particularly in young children who are unable to verbalize symptoms. Clinical evaluation, including assessment for systemic signs such as fever and poor feeding, along with UA and imaging studies, are essential in making this differentiation.[47,193] While infections are mainly caused by gram-negative bacteria, noninfectious causes also contribute to the diagnostic challenge. Prevention of long-term kidney damage from pyelonephritis necessitates prompt recognition and treatment, considering genetic, urinary, and environmental factors.

Question 31: What Is the Optimal Follow-Up Timeframe for Pediatric Patients With UTI?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Observational data suggests that clinical improvement, including fever resolution, typically occurs after 48 to 72 hours of treatment in children.[194,195] Authors believe it to be reasonable to conduct additional work-up (eg, kidney and bladder ultrasonography) and/or reassess the current treatment plan if patients do not experience clinical improvement within that timeframe.[194,196-200] Assuming the patient improves as expected, previously described treatment durations of 3 to 5 days for cystitis and 7 to 10 days for pyelonephritis are reasonable (more detail in questions 19 and 20). Routine follow-up is not necessary unless the patient is younger than age 2 years and experiences a febrile UTI or a child of any age experiences a recurrence of febrile UTI. It is reasonable to deescalate and/or target treatment as soon as culture and susceptibility results are available based on the discussion in question 27 and other studies of children who are hospitalized.[201,202]

Question 32: For Kidney Transplant Recipients, What Is the Significance of a Positive Urine Culture?

The clinical review found insufficient quality of evidence to enable a clear recommendation. UTIs are an important postkidney transplant complication.[203,204] The spectrum of causative microorganisms is broad and includes typical uropathogens, atypical pathogens, and MDROs.[205] This complexity demands a nuanced understanding of microbial behavior in the context of immunosuppressed individuals. Cultures need to be interpreted within their clinical context, including specific timing posttransplantation and symptoms. Routine treatment of ASB in kidney transplant recipients increases colonization with resistant organisms without providing clear benefit and should be avoided after the first 2 months from transplantation.[206]

Question 33: What Is the Empirical and Definitive Treatment of Emphysematous Cystitis and Pyelonephritis?

The clinical review found insufficient quality of evidence to enable a clear recommendation. The treatment of emphysematous cystitis and pyelonephritis (caused by gas producing pathogens) lacks robust data, with recommendations mostly relying on clinical judgment and case studies.[207] Early appropriate antibiotics targeting common pathogens like *Escherichia coli* and *Klebsiella* species is reasonable, with a general treatment approach mirroring that for nonemphysematous UTIs.[208] While most cases respond to medical therapy, severe instances may need surgical intervention.

Percutaneous catheter drainage, along with antibiotics, shows lower mortality for emphysematous pyelonephritis and is advisable in severe cases to include broader coverage until culture results are available.[209] Most authors believe a treatment duration of 7 to 14 days (adjusted per clinical response) is reasonable.[210]

Question 34: What Is the Clinical Presentation and Diagnostic Approach for Kidney or Perinephric Abscess? What Is the Empirical and Definitive Treatment of Kidney Abscess and Perinephric Abscess?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Perinephric abscesses are serious conditions with varied presentations.[211] Typical symptoms include lumbar pain and fever, with many patients presenting with costovertebral angle tenderness. CT imaging is crucial for diagnosis and management, which may include medical therapy, percutaneous drainage, or surgery for refractory cases.[211] These abscesses are commonly caused by gram-negative bacteria or hematogenous seeding from organisms like *Staphylococcus aureus*. Decision to opt for drainage of the abscess is often influenced by the size,[212,213] however, some form of drainage is often necessary for definitive treatment. Further research is needed on optimal source control intervention strategies and when medical management alone may be used.[214-216]

Question 35: What Is the Clinical Presentation, Diagnostic Approach, and Treatment for Acute and Chronic Prostatitis?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP) are inflammatory prostate syndromes with ABP often presenting abruptly with febrile UTI symptoms and CBP involving more persistent symptoms or recurrent UTIs.[217,218] Diagnosis for ABP relies on clinical presentation and laboratory tests. CBP diagnosis involves comparing bacteria levels in prostatic fluid and urinary cultures, yet definitive testing is debated. Testing for prostate specific antigen (PSA) appears of limited utility.[219] Maneuvers to express prostatic fluid, such as prostate massage, are of limited clinical utility and urology consultation may be needed.[219,220] The optimal durations of treatment for ABP or CBP are unknown and have not been established by high-quality studies. Additional prospective studies are needed to determine the appropriate duration of treatment for ABP and CBP.

Question 37: What Are Nonbacterial Causes of UTI to Consider in Certain Special Populations?

The clinical review found insufficient quality of evidence to enable a clear recommendation. Most nonbacterial UTIs are due to *Candida* species[230] While 25% of intensive care unit UTIs in the US are attributed to *Candida* species, most cases of candiduria are asymptomatic and benign. If symptomatic, fluconazole and amphotericin B are preferred due to favorable urinary pharmacokinetics and pharmacodynamics, but no RCTs are available to determine the best treatment choice or duration.[230,231] Viral UTIs (especially BK polyomavirus and adenovirus) are less common but a noteworthy risk in immunocompromised patients.[232-234] A reduction in the intensity of existing immunosuppression is the primary treatment. Small case reports detail individual experiences with antivirals with in vitro activity against these viruses exist, but their retrospective nature and small size limit generalizability.[235-237]

Question 36: What Is the Optimal Clinical Approach for Patients With Nephrolithiasis, Foreign Objects, Nephrostomy Tubes, and/or Ureteral Stents?

A sufficient quality and quantity of evidence was found to provide a clear recommendation for the optimal clinical approach for patients with nephrolithiasis, foreign objects, nephrostomy tubes, and/or ureteral stents. Routine cystoscopy and urodynamic studies do not require antimicrobial prophylaxis in asymptomatic patients. Preoperative antibiotics do not appear to reduce infectious complications from routine cystoscopic stent removal nor nephrostomy tube placement.[221,222] The majority of patients with uncomplicated urologic cases undergoing percutaneous nephrolithotomy, a

single dose of antimicrobial prophylaxis appears to reduce the risk of infection.[158,223-225] However, in a recent meta-analysis,[226] single dose was found to be associated with higher rates of systemic inflammatory response syndrome (SIRS) postnephrolithotomy compared with extended perioperative dosing in patients considered high risk; however, the use of a nonspecific measure, such as SIRS, to detect complications may overidentify complications.[227] If there are particularly vulnerable patients, such as in pregnancy or kidney transplant, extended preoperative dosing schedules are reasonable to consider. Published RCTs use a 7-day duration preoperatively, however, it is unclear if that long of a course is routinely necessary.[228,229]

Discussion

Despite decades of research and nearly 1000 studies reviewed, we remain unable to provide a clear recommendation on many, even some essential, aspects of the prevention, diagnosis, and treatment of urinary tract infections. This consensus statement highlights the dramatic impact of historical practice patterns on certain aspects of UTI treatment, such as duration of therapy, while also highlighting critical gaps in knowledge that impact our understanding of how effective our treatments are, such as the impact of clinical improvement without resolution of bacteriuria. Additionally, there is an obvious need to use more precise terminology to describe site(s) and extent of infections rather than the vague terms that have become commonplace in clinical practice. This will ensure that there are more clearly defined study populations, reduced heterogeneity in generalizability of those studies, and ensure that individual patients receive the highest value, most appropriate care for their specific infection.

Limitations

This consensus statement has limitations. The main limitation of this guideline is the overall dearth of hypothesis-confirming evidence. Using the WikiGuidelines method of guideline development, only 6 clear recommendations were able to be established out of 37 questions, highlighting the need for additional high-quality prospective studies in all aspects of the management of urinary tract infections. Additionally, certain sections of the article may be less generalizable than others, such as in the empiric treatment section, which is heavily influenced by local epidemiology. Despite these limitations, we attempted to equip readers with the foundational principles that they may apply to their individual practice settings. We made an effort within this guideline to include experts internationally; however, most of the guideline authors are from high-income countries and in the future, we hope to incorporate the essential perspective of and thus provide guidance for clinicians practicing in low and middle-income countries and other resource-constrained settings.

Conclusions

This consensus statement presents evidence-based strategies for managing UTIs and clinical reviews in areas where strong evidence is lacking. The guidance is based on information available up to early 2024. Pressing research gaps remain, including the need for high-quality studies to validate novel diagnostic methods, optimize treatment durations, establish standard definitions, and refine antimicrobial stewardship strategies for asymptomatic bacteriuria and MDROs. Suggestions for alternative evidence or recommendations are welcome for consideration by the authors, with updates to the guideline made as needed. No single guideline can encompass all clinical scenarios; therefore, this document is not intended to set legal medical standards or replace professional judgment for individual patient cases.

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REFERENCES

1. Stapleton A, Latham RH, Johnson C, Stamm WE. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection: a randomized, double-blind, placebo-controlled trial. *JAMA*. 1990;264(6):703-706. doi:10.1001/jama.1990.03450060049027

2. Melekos MD, Asbach HW, Gerharz E, Zarakovitis IE, Weingaertner K, Naber KG. Post-intercourse versus daily ciprofloxacin prophylaxis for recurrent urinary tract infections in premenopausal women. *J Urol*. 1997;157(3):935-939. doi:10.1016/S0022-5347(01)65087-0

3. Jent P, Berger J, Kuhn A, Trautner BW, Atkinson A, Marschall J. Antibiotics for preventing recurrent urinary tract infection: systematic review and meta-analysis. *Open Forum Infect Dis*. 2022;9(7):ofac327. doi:10.1093/ofid/ofac327

4. Buettcher M, Trueck J, Niederer-Loher A, et al. Swiss consensus recommendations on urinary tract infections in children. *Eur J Pediatr*. 2021;180(3):663-674. doi:10.1007/s00431-020-03714-4

5. Autore G, Bernardi L, Ghidini F, et al; The Uti-Ped-Er Study Group. Antibiotic prophylaxis for the prevention of urinary tract infections in children: guideline and recommendations from the Emilia-Romagna Pediatric Urinary Tract Infections (UTI-Ped-ER) study group. *Antibiotics (Basel)*. 2023;12(6):1040. doi:10.3390/antibiotics12061040

6. Mattoo TK, Shaikh N, Nelson CP. Contemporary management of urinary tract infection in children. *Pediatrics*. 2021;147(2):e2020012138. doi:10.1542/peds.2020-012138

7. McGuinness SD, Krone R, Metz LMA. Double-blind, randomized, placebo-controlled trial of cranberry supplements in multiple sclerosis. *J Neurosci Nurs*. 2002;34(1):4. doi:10.1097/01376517-200202000-00002

8. Cowan CC, Hutchison C, Cole T, 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. *Clin Oncol (R Coll Radiol)*. 2012;24(2):e31-e38. doi:10.1016/j.clon.2011.05.009

9. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol*. 2002;9(3):1558-1562.

10. 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. *Am J Clin Nutr*. 2016;103(6):1434-1442. doi:10.3945/ajcn.116.130542

11. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10(10):CD001321. doi:10.1002/14651858.CD001321.pub5

12. Mantzorou M, Giaginis C. Cranberry consumption against urinary tract infections: clinical stateof- the-art and future perspectives. *Curr Pharm Biotechnol*. 2018;19(13):1049-1063. doi:10.2174/1389201020666181206104129

13. Foxman B, Cronenwett AEW, Spino C, Berger MB, Morgan DM. Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. *Am J Obstet Gynecol*. 2015;213(2):194.e1-194.e8. doi:10.1016/j.ajog.2015.04.003

14. 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. *Clin Infect Dis*. 2011;52(1):23-30. doi:10.1093/cid/ciq073

15. McMurdo MET, 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. *J Antimicrob Chemother*. 2009;63(2):389-395. doi:10.1093/jac/dkn489

16. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. *J Urol*. 2008;180(4):1367-1372. doi:10.1016/j.juro.2008.06.016

17. McMurdo MET, Bissett LY, Price RJG, 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):256-261. doi:10.1093/ageing/afi101

18. 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. *J Spinal Cord Med*. 2004;27(1):29-34. doi:10.1080/10790268.2004.11753727

19. Babar A, Moore L, Leblanc V, 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 Urol*. 2021;21(1):44. doi:10.1186/s12894-021-00811-w

20. 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. doi:10.1136/bmj.322.7302.1571

21. Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc*. 2012;87(2):143-150. doi:10.1016/j.mayocp.2011.10.006

22. Di Martino P, Agniel R, David K, et al. Reduction of Escherichia coli adherence to uroepithelial bladder cells after consumption of cranberry juice: a double-blind randomized placebo-controlled cross-over trial. *World J Urol*. 2006;24(1):21-27. doi:10.1007/s00345-005-0045-z

23. Lee BB, Haran MJ, Hunt LM, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. *Spinal Cord*. 2007;45(8):542-550. doi:10.1038/sj.sc.3101974

24. Hooton TM, Vecchio M, Iroz A, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. *JAMA Intern Med*. 2018;178(11):1509-1515. doi:10.1001/jamainternmed.2018.4204

25. Mentes JC, Culp K. Reducing hydration-linked events in nursing home residents. *Clin Nurs Res*. 2003;12(3):210-225. doi:10.1177/1054773803252996

26. Tan-Kim J, Shah NM, Do D, Menefee SA. Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women. *Am J Obstet Gynecol*. 2023;229(2):143.e1-143.e9. doi:10.1016/j.ajog.2023.05.002

27. Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis*. 2007;195(5):623-624. doi:10.1086/511526

28. Simunić V, Banović I, Ciglar S, Jeren L, Pavicić Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet*. 2003;82(2):187-197. doi:10.1016/S0020-7292(03)00200-5

29. McVicker L, Labeit AM, Coupland CAC, et al. Vaginal estrogen therapy use and survival in females with breast cancer. *JAMA Oncol*. 2024;10(1):103-108. doi:10.1001/jamaoncol.2023.4508

30. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*. 2018;25(1):11-20. doi:10.1097/GME.0000000000000956

31. Harding C, Chadwick T, Homer T, et al. Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. *Health Technol Assess*. 2022;26(23):1-172. doi:10.3310/QOIZ6538

32. Botros C, Lozo S, Iyer S, et al. Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial. *Int Urogynecol J*. 2022;33(3):571-580. doi:10.1007/s00192-021-04849-0

33. Wolff BJ, Price TK, Joyce CJ, Wolfe AJ, Mueller ER. Oral probiotics and the female urinary microbiome: a double-blinded randomized placebo-controlled trial. *Int Urol Nephrol*. 2019;51(12):2149-2159. doi:10.1007/s11255-019-02282-3

34. Toh SL, Boswell-Ruys CL, Lee BSB, Simpson JM, Clezy KR. Probiotics for preventing urinary tract infection in people with neuropathic bladder. *Cochrane Database Syst Rev*. 2017;9(9):CD010723. doi:10.1002/14651858.CD010723.pub2

35. Toh SL, Lee BB, Ryan S, et al. Probiotics [LGG-BB12 or RC14-GR1] versus placebo as prophylaxis for urinary tract infection in persons with spinal cord injury [ProSCIUTTU]: a randomised controlled trial. *Spinal Cord*. 2019;57(7):550-561. doi:10.1038/s41393-019-0251-y

36. Abdullatif VA, Sur RL, Eshaghian E, et al. Efficacy of probiotics as prophylaxis for urinary tract infections in premenopausal women: a systematic review and meta-analysis. *Cureus*. 2021;13(10):e18843. doi:10.7759/cureus.18843

37. Ala-Jaakkola R, Laitila A, Ouwehand AC, Lehtoranta L. Role of D-mannose in urinary tract infections—a narrative review. *Nutr J*. 2022;21(1):18. doi:10.1186/s12937-022-00769-x

38. Porru D, Parmigiani A, Tinelli C, et al. Oral D-mannose in recurrent urinary tract infections in women: a pilot study. *J Clin Urol*. 2014;7(3):208-213. doi:10.1177/2051415813518332

39. Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*. 2014;32(1):79-84. doi:10.1007/s00345-013-1091-6

40. Hayward G, Mort S, Hay AD, et al. D-mannose for prevention of recurrent urinary tract infection among women: a randomized clinical trial. *JAMA Intern Med*. 2024;184(6):619-628. doi:10.1001/jamainternmed.2024.0264

41. Phé V, Pakzad M, Haslam C, et al. Open label feasibility study evaluating D-mannose combined with home-based monitoring of suspected urinary tract infections in patients with multiple sclerosis. *Neurourol Urodyn*. 2017;36(7):1770-1775. doi:10.1002/nau.23173

42. Domenici L, Monti M, Bracchi C, et al. D-mannose: a promising support for acute urinary tract infections in women: a pilot study. *Eur Rev Med Pharmacol Sci*. 2016;20(13):2920-2925.

43. Cooper TE, Teng C, Howell M, Teixeira-Pinto A, Jaure A, Wong G. D-mannose for preventing and treating urinary tract infections. *Cochrane Database Syst Rev*. 2022;8(8):CD013608. doi:10.1002/14651858.CD013608.pub2

44. Lenger SM, Bradley MS, Thomas DA, Bertolet MH, Lowder JL, Sutcliffe S. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;223(2):265.e1-265.e13. doi:10.1016/j.ajog.2020.05.048

45. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. *Am Fam Physician*. 2005;71(6):1153-1162.

46. Advani SD, Polage CR, Fakih MG. Deconstructing the urinalysis: a novel approach to diagnostic and antimicrobial stewardship. *Antimicrob Steward Healthc Epidemiol*. 2021;1(1):e6. doi:10.1017/ash.2021.167

47. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. 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. doi:10.1542/peds.2011-1330

48. Bhat RG, Katy TA, Place FC. Pediatric urinary tract infections. *Emerg Med Clin North Am*. 2011;29(3):637-653. doi:10.1016/j.emc.2011.04.004

49. Mena Lora AJ, Hua J, Ali M, Krill C, Takhsh E, Bleasdale SC. Changing the culture: impact of a diagnostic stewardship intervention for urine culture testing and CAUTI prevention in an urban safety-net community hospital. *Antimicrob Steward Healthc Epidemiol*. 2024;4(1):e14. doi:10.1017/ash.2024.12

50. Werneburg GT, Rhoads DD. Diagnostic stewardship for urinary tract infection: a snapshot of the expert guidance. *Cleve Clin J Med*. 2022;89(10):581-587. doi:10.3949/ccjm.89a.22008

51. O'Grady NP, Alexander E, Alhazzani W, et al. Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for evaluating new fever in adult patients in the ICU. *Crit Care Med*. 2023;51(11):1570-1586. doi:10.1097/CCM.0000000000006022

52. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*. 2005;40(5):643-654. doi:10.1086/427507

53. Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):1611-1615. doi:10.1093/cid/ciz021

54. Flokas ME, Andreatos N, Alevizakos M, Kalbasi A, Onur P, Mylonakis E. Inappropriate management of asymptomatic patients with positive urine cultures: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2017;4(4):ofx207. doi:10.1093/ofid/ofx207

55. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med*. 1982;307(8):463-468. doi:10.1056/NEJM198208193070802

56. Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med*. 2013;369(20):1883-1891. doi:10.1056/NEJMoa1302186

57. Tullus K. Defining urinary tract infection by bacterial colony counts: a case for less than 100,000 colonies/mL as the threshold. *Pediatr Nephrol*. 2019;34(10):1651-1653. doi:10.1007/s00467-019-04291-x

58. Kass EH. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians*. 1956;69:56-64.

59. Szlachta-McGinn A, Douglass KM, Chung UYR, Jackson NJ, Nickel JC, Ackerman AL. Molecular diagnostic methods versus conventional urine culture for diagnosis and treatment of urinary tract infection: a systematic review and meta-analysis. *Eur Urol Open Sci*. 2022;44:113-124. doi:10.1016/j.euros.2022.08.009

60. Hilt EE, McKinley K, Pearce MM, et al. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. *J Clin Microbiol*. 2014;52(3):871-876. doi:10.1128/JCM.02876-13

61. Lewis DA, Gumede LYE, van der Hoven LA, et al. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. *S Afr Med J*. 2013;103(6):377-381. doi:10.7196/SAMJ.6722

62. Wolfe AJ, Toh E, Shibata N, et al. Evidence of uncultivated bacteria in the adult female bladder. *J Clin Microbiol*. 2012;50(4):1376-1383. doi:10.1128/JCM.05852-11

63. Hugon P, Dufour JC, Colson P, Fournier PE, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. *Lancet Infect Dis*. 2015;15(10):1211-1219. doi:10.1016/S1473-3099(15)00293-5

64. Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. *mBio*. 2020;11(2):e00218-e00220. doi:10.1128/mBio.00218-20

65. Kim Y, Seo MR, Kim SJ, et al. Usefulness of blood cultures and radiologic imaging studies in the management of patients with community-acquired acute pyelonephritis. *Infect Chemother*. 2017;49(1):22-30. doi:10.3947/ic.2017.49.1.22

66. Soulen MC, Fishman EK, Goldman SM, Gatewood OM. Bacterial renal infection: role of CT. *Radiology*. 1989;171(3):703-707. doi:10.1148/radiology.171.3.2655002

67. Pierce C, Keniston A, Albert RK. Imaging in acute pyelonephritis: utilization, findings, and effect on management. *South Med J*. 2019;112(2):118-124. doi:10.14423/SMJ.0000000000000936

68. Enikeev DV, Glybochko P, Alyaev Y, Enikeev M, Rapoport L. Imaging technologies in the diagnosis and treatment of acute pyelonephritis. *Urologia*. 2017;84(3):179-184. doi:10.5301/uj.5000234

69. Johnson JR, Russo TA. Acute pyelonephritis in adults. *N Engl J Med*. 2018;378(1):48-59. doi:10.1056/NEJMcp1702758

70. Faletti R, Cassinis MC, Fonio P, et al. Diffusion-weighted imaging and apparent diffusion coefficient values versus contrast-enhanced MR imaging in the identification and characterisation of acute pyelonephritis. *Eur Radiol*. 2013;23(12):3501-3508. doi:10.1007/s00330-013-2951-6

71. Leyendecker JR, Clingan MJ. Magnetic resonance urography update—are we there yet? *Semin Ultrasound CT MR*. 2009;30(4):246-257. doi:10.1053/j.sult.2009.03.004

72. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med*. 2000;160(5):673-677. doi:10.1001/archinte.160.5.673

73. Warren JW, Tenney JH, Hoopes JM, Muncie HL, Anthony WC. A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. *J Infect Dis*. 1982;146(6):719-723. doi:10.1093/infdis/146.6.719

74. Abdel-Latif M, Mosbah A, El Bahnasawy MS, Elsawy E, Shaaban AA. Asymptomatic bacteriuria in men with orthotopic ileal neobladders: possible relationship to nocturnal enuresis. *BJU Int*. 2005;96(3):391-396. doi:10.1111/j.1464-410X.2005.05637.x

75. Morris EJ, Bracken RB, Hopfer RL, Mills K, Rodriguez DB. Urinary findings in 20 asymptomatic patients with an ileal conduit. *J Enterostomal Ther*. 1982;9(2):24-27. doi:10.1097/00152192-198203000-00022

76. Gupta K, Hooton TM, Naber KG, et al; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-e120. doi:10.1093/cid/ciq257

77. Hooton TM, Bradley SF, Cardenas DD, et al; Infectious Diseases Society of America. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(5):625-663. doi:10.1086/650482

78. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. *JAMA*. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627

79. Park DW, Peck KR, Chung MH, et al. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. *J Korean Med Sci*. 2012;27(5):476-483. doi:10.3346/jkms.2012.27.5.476

80. Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial resistance trends in urine escherichia coli isolates from adult and adolescent females in the United States from 2011 to 2019: rising ESBL strains and impact on patient management. *Clin Infect Dis*. 2021;73(11):1992-1999. doi:10.1093/cid/ciab560

81. Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. *J Urol*. 2000;164(4):1254-1258. doi:10.1016/S0022-5347(05)67150-9

82. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: a systematic literature review. *Saudi Pharm J*. 2018;26(5):678-684. doi:10.1016/j.jsps.2018.02.023

83. Larramendy S, Deglaire V, Dusollier P, et al. Risk factors of extended-spectrum beta-lactamases-producing *Escherichia coli* community acquired urinary tract infections: a systematic review. *Infect Drug Resist*. 2020;13:3945-3955. doi:10.2147/IDR.S269033

84. Brown DG, Worby CJ, Pender MA, et al. Development of a prediction model for the acquisition of extended spectrum beta-lactam-resistant organisms in US international travellers. *J Travel Med*. 2023;30(6):taad028. doi:10.1093/jtm/taad028

85. Kadry N, Natarajan M, Bein E, Kim P, Farley J. discordant clinical and microbiological outcomes are associated with late clinical relapse in clinical trials for complicated urinary tract infections. *Clin Infect Dis*. 2023;76(10):1768-1775. doi:10.1093/cid/ciad010

86. Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children: the SCOUT randomized clinical trial. *JAMA Pediatr*. 2023;177(8):782-789. doi:10.1001/jamapediatrics.2023.1979

87. Lafaurie M, Chevret S, Fontaine JP, et al; PROSTASHORT Study Group. Antimicrobial for 7 or 14 days for febrile urinary tract infection in men: a multicenter noninferiority double-blind, placebo-controlled, randomized clinical trial. *Clin Infect Dis*. 2023;76(12):2154-2162. doi:10.1093/cid/ciad070

88. Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. *J Antimicrob Chemother*. 2001;48(6):895-901. doi:10.1093/jac/48.6.895

89. Efstathiou SP, Pefanis AV, Tsioulos DI, et al. Acute pyelonephritis in adults: prediction of mortality and failure of treatment. *Arch Intern Med*. 2003;163(10):1206-1212. doi:10.1001/archinte.163.10.1206

90. Pertel PE, Haverstock D. Risk factors for a poor outcome after therapy for acute pyelonephritis. *BJU Int*. 2006;98(1):141-147. doi:10.1111/j.1464-410X.2006.06222.x

91. Karve S, Ryan K, Peeters P, et al. The impact of initial antibiotic treatment failure: real-world insights in patients with complicated urinary tract infection. *J Infect*. 2018;76(2):121-131. doi:10.1016/j.jinf.2017.11.001

92. Rosa R, Abbo LM, Raney K, Tookes HE III, Supino M. Antimicrobial resistance in urinary tract infections at a large urban ED: factors contributing to empiric treatment failure. *Am J Emerg Med*. 2017;35(3):397-401. doi:10.1016/j.ajem.2016.11.021

93. Jorgensen S, Zurayk M, Yeung S, et al. Risk factors for early return visits to the emergency department in patients with urinary tract infection. *Am J Emerg Med*. 2018;36(1):12-17. doi:10.1016/j.ajem.2017.06.041

94. Pujades-Rodriguez M, West RM, Wilcox MH, Sandoe J. Lower urinary tract infections: management, outcomes and risk factors for antibiotic re-prescription in primary care. *EClinicalMedicine*. 2019;14:23-31. doi:10.1016/j.eclinm.2019.07.012

95. Eliakim-Raz N, Babitch T, Shaw E, et al; RESCUING Study Group. Risk factors for treatment failure and mortality among hospitalized patients with complicated urinary tract infection: a multicenter retrospective cohort study (RESCUING study group). *Clin Infect Dis*. 2019;68(1):29-36. doi:10.1093/cid/ciy418

96. Martischang R, Godycki-Ćwirko M, Kowalczyk A, et al. Risk factors for treatment failure in women with uncomplicated lower urinary tract infection. *PLoS One*. 2021;16(8):e0256464. doi:10.1371/journal.pone.0256464

97. Trautner BW, Kaye KS, Gupta V, et al. Risk factors associated with antimicrobial resistance and adverse short-term health outcomes among adult and adolescent female outpatients with uncomplicated urinary tract infection. *Open Forum Infect Dis*. 2022;9(12):ofac623. doi:10.1093/ofid/ofac623

98. Dunne MW, Puttagunta S, Aronin SI, Brossette S, Murray J, Gupta V. Impact of empirical antibiotic therapy on outcomes of outpatient urinary tract infection due to nonsusceptible *Enterobacterales*. *Microbiol Spectr*. 2022;10(1):e0235921. doi:10.1128/spectrum.02359-21

99. Lamas Ferreiro JL, Álvarez Otero J, González González L, et al. Pseudomonas aeruginosa urinary tract infections in hospitalized patients: mortality and prognostic factors. *PLoS One*. 2017;12(5):e0178178. doi:10.1371/journal.pone.0178178

100. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. *Cochrane Database Syst Rev*. 2003;(1):CD003966. doi:10.1002/14651858.CD003966

101. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. *Cochrane Database Syst Rev*. 2012;2012(8):CD006857. doi:10.1002/14651858.CD006857.pub2

102. Moreira MVB, de Freitas LR, Fonseca LM, et al. Shorter versus longer-course of antibiotic therapy for urinary tract infections in pediatric population: an updated meta-analysis. *Eur J Pediatr*. 2024;183(5):2037-2047. doi:10.1007/s00431-024-05512-8

103. Goodlet KJ, Benhalima FZ, Nailor MD. A systematic review of single-dose aminoglycoside therapy for urinary tract infection: is it time to resurrect an old strategy? *Antimicrob Agents Chemother*. 2018;63(1):e02165-e18. doi:10.1128/AAC.02165-18

104. Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*. 2014;7. doi:10.1002/14651858.CD003772.pub4

105. Montini G, Tessitore A, Console K, Ronfani L, Barbi E, Pennesi M; STOP Trial Group. Short oral antibiotic therapy for pediatric febrile urinary tract infections: a randomized trial. *Pediatrics*. 2024;153(1):e2023062598. doi:10.1542/peds.2023-062598

106. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative effectiveness of antibiotic treatment duration in children with pyelonephritis. *JAMA Netw Open*. 2020;3(5):e203951. doi:10.1001/jamanetworkopen.2020.3951

107. Afolabi TM, Goodlet KJ, Fairman KA. Association of antibiotic treatment duration with recurrence of uncomplicated urinary tract infection in pediatric patients. *Ann Pharmacother*. 2020;54(8):757-766. doi:10.1177/1060028019900650

108. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother*. 2015;70(9):2456-2464. doi:10.1093/jac/dkv147

109. Kim DK, Kim JH, Lee JY, 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 trials. *Lancet Infect Dis*. 2020;20(9):1080-1088. doi:10.1016/S1473-3099(20)30121-3

110. 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(482):729-734.

111. Trienekens TA, Stobberingh EE, Winkens RA, Houben AW. Different lengths of treatment with co-trimoxazole for acute uncomplicated urinary tract infections in women. *BMJ*. 1989;299(6711):1319-1322. doi:10.1136/bmj.299.6711.1319

112. Gossius G, Vorland L. A randomised comparison of single-dose vs three-day and ten-day therapy with trimethoprim-sulfamethoxazole for acute cystitis in women. *Scand J Infect Dis*. 1984;16(4):373-379. doi:10.3109/00365548409073963

113. Hooton TM, Latham RH, Wong ES, Johnson C, Roberts PL, Stamm WE. Ofloxacin versus trimethoprim-sulfamethoxazole for treatment of acute cystitis. *Antimicrob Agents Chemother*. 1989;33(8):1308-1312. doi:10.1128/AAC.33.8.1308

114. Neringer R, Forsgren A, Hansson C, Ode B; The South Swedish Lolex Study Group. Lomefloxacin versus norfloxacin in the treatment of uncomplicated urinary tract infections: three-day versus seven-day treatment. *Scand J Infect Dis*. 1992;24(6):773-780. doi:10.3109/00365549209062463

115. Trienekens TA, London NH, Houben AW, De Jong RA, Stobberingh EE. Treating acute urinary tract infections: an RCT of 3-day versus 7-day norfloxacin. *Can Fam Physician*. 1993;39:514-518.

116. Arredondo-García JL, Figueroa-Damián R, Rosas A, et al; uUTI Latin American Study Group. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *J Antimicrob Chemother*. 2004;54(4):840-843. doi:10.1093/jac/dkh414

117. Vogel T, Verreault R, Gourdeau M, Morin M, Grenier-Gosselin L, Rochette L. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. *CMAJ*. 2004;170(4):469-473.

118. Bahman H, Hyaide O, Omid N, et al. Comparison of 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated urinary tract infection in women: a randomized double-blind clinical trial. *Iranian J Clin Infect Dis*. 2010;55(2):70-74.

119. Boerema JB, Willems FT. Fosfomycin trometamol in a single dose versus norfloxacin for seven days in the treatment of uncomplicated urinary infections in general practice. *Infection*. 1990;18(suppl 2):S80-S88. doi:10.1007/BF01643433

120. Crocchiolo P; Multicenter Group of General Practitioners. Single-dose fosfomycin trometamol versus multiple-dose cotrimoxazole in the treatment of lower urinary tract infections in general practice. *Chemotherapy*. 1990;36(suppl 1):37-40. doi:10.1159/000238815

121. Selvaggi FP, Ditonno P, Traficante A, Battaglia M, Di Lorenzo V. Fosfomycin trometamol (Monuril) versus norfloxacin in single dose for adult female uncomplicated UTIs: multicenter randomized, double-blind study. *Chemotherapy*. 1990;36(suppl 1):31-33. doi:10.1159/000238813

122. Naber KG, Thyroff-Friesinger U. Fosfomycin trometamol versus ofloxacin/co-trimoxazole as single dose therapy of acute uncomplicated urinary tract infection in females: a multicentre study. *Infection*. 1990;18(suppl 2):S70-S76. doi:10.1007/BF01643431

123. de Jong Z, Pontonnier F, Plante P. Single-dose fosfomycin trometamol (Monuril) versus multiple-dose norfloxacin: results of a multicenter study in females with uncomplicated lower urinary tract infections. *Urol Int*. 1991;46(4):344-348. doi:10.1159/000282164

124. Van Pienbroek E, Hermans J, Kaptein AA, Mulder JD. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharm World Sci*. 1993;15(6):257-262. doi:10.1007/BF01871127

125. Elhanan G, Tabenkin H, Yahalom R, Raz R. Single-dose fosfomycin trometamol versus 5-day cephalexin regimen for treatment of uncomplicated lower urinary tract infections in women. *Antimicrob Agents Chemother*. 1994;38(11):2612-2614. doi:10.1128/AAC.38.11.2612

126. Minassian MA, Lewis DA, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. *Int J Antimicrob Agents*. 1998;10(1):39-47. doi:10.1016/S0924-8579(98)00021-1

127. Ceran N, Mert D, Kocdogan FY, et al. A randomized comparative study of single-dose fosfomycin and 5-day ciprofloxacin in female patients with uncomplicated lower urinary tract infections. *J Infect Chemother*. 2010;16(6):424-430. doi:10.1007/s10156-010-0079-z

128. PIVYA. Highlights of prescribing information. US Food and Drug Administration; 2024. Accessed May 25, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216483s000lbl.pdf

129. Richards HH. Comparative efficacy of 3-day and 7-day chemotherapy with twice-daily pivmecillinam in urinary tract infections seen in general practice. *Curr Med Res Opin*. 1984;9(3):197-203. doi:10.1185/03007998409109580

130. Pitkäjärvi T, Pyykönen ML, Kannisto K, Piippo T, Viita P. Pivmecillinam treatment in acute cystitis: three versus seven days study. *Arzneimittelforschung*. 1990;40(10):1156-1158.

131. 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(1):49-57. doi:10.1080/02813430601183074

132. Jansåker F, Thønnings S, Hertz FB, et al. Three versus five days of pivmecillinam for community-acquired uncomplicated lower urinary tract infection: a randomised, double-blind, placebo-controlled superiority trial. *EClinicalMedicine*. 2019;12:62-69. doi:10.1016/j.eclinm.2019.06.009

133. Wagenlehner F, Perry CR, Hooton TM, et al. Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials. *Lancet*. 2024;403(10428):741-755. doi:10.1016/S0140-6736(23)02196-7

134. Dinh A, Davido B, Etienne M, et al. Is 5 days of oral fluoroquinolone enough for acute uncomplicated pyelonephritis? The DTP randomized trial. *Eur J Clin Microbiol Infect Dis*. 2017;36(8):1443-1448. doi:10.1007/s10096-017-2951-6

135. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology*. 2008;71(1):17-22. doi:10.1016/j.urology.2007.09.002

136. Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. *Curr Med Res Opin*. 2007;23(11):2637-2645. doi:10.1185/030079907X233340

137. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection–7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2013;68(10):2183-2191. doi:10.1093/jac/dkt177

138. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA*. 2000;283(12):1583-1590. doi:10.1001/jama.283.12.1583

139. 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(9840):484-490. doi:10.1016/S0140-6736(12)60608-4

140. Ode B, Bröms M, Walder M, Cronberg S. Failure of excessive doses of ampicillin to prevent bacterial relapse in the treatment of acute pyelonephritis. *Acta Med Scand*. 1980;207(4):305-307. doi:10.1111/j.0954-6820.1980.tb09725.x

141. Jernelius H, Zbornik J, Bauer CA. One or three weeks' treatment of acute pyelonephritis: a double-blind comparison, using a fixed combination of pivampicillin plus pivmecillinam. *Acta Med Scand*. 1988;223(5):469-477. doi:10.1111/j.0954-6820.1988.tb15899.x

142. Mensa J, Moreno-Martinez A, Martinez J. Treatment of acute uncomplicated pyelonephritis (AUP): a randomized trial comparing 7- vs. 14-day therapy. Presented at: American Society for Microbiology Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 1999; San Francisco, CA.

143. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet*. 2015;385(9981):1949-1956. doi:10.1016/S0140-6736(14)62220-0

144. Langford BJ, Daneman N, Diong C, et al. Antibiotic Selection and duration for catheter-associated urinary tract infection in non-hospitalized older adults: a population-based cohort study. *Antimicrob Steward Healthc Epidemiol*. 2023;3(1):e132. doi:10.1017/ash.2023.176

145. Yahav D, Franceschini E, Koppel F, et al; Bacteremia Duration Study Group. Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial. *Clin Infect Dis*. 2019;69(7):1091-1098. doi:10.1093/cid/ciy1054

146. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. *JAMA*. 2020;323(21):2160-2169. doi:10.1001/jama.2020.6348

147. Molina J, Montero-Mateos E, Praena-Segovia J, et al; SHORTEN trial team. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. *Clin Microbiol Infect*. 2022;28(4):550-557. doi:10.1016/j.cmi.2021.09.001

148. Turjeman A, von Dach E, Molina J, et al. Duration of antibiotic treatment for gram-negative bacteremia—systematic review and individual participant data (IPD) meta-analysis. *EClinicalMedicine*. 2022;55:101750. doi:10.1016/j.eclinm.2022.101750

149. Al Lawati H, Blair BM, Larnard J. Urinary tract infections: core curriculum 2024. *Am J Kidney Dis*. 2024;83(1):90-100. doi:10.1053/j.ajkd.2023.08.009

150. Liu F, MacDonald B, Jain R, et al. Prevalence and treatment of asymptomatic bacteriuria at academic and critical-access hospitals—opportunities for stewardship efforts. *Infect Control Hosp Epidemiol*. 2023;44(6):979-981. doi:10.1017/ice.2022.143

151. Petty LA, Vaughn VM, Flanders SA, et al. Risk factors and outcomes associated with treatment of asymptomatic bacteriuria in hospitalized patients. *JAMA Intern Med*. 2019;179(11):1519-1527. doi:10.1001/jamainternmed.2019.2871

152. Petty LA, Vaughn VM, Flanders SA, et al. Assessment of testing and treatment of asymptomatic bacteriuria initiated in the emergency department. *Open Forum Infect Dis*. 2020;7(12):ofaa537. doi:10.1093/ofid/ofaa537

153. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2019;2019(11):CD000490. doi:10.1002/14651858.CD000490.pub4

154. Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2019;322(12):1195-1205. doi:10.1001/jama.2019.10060

155. Grabe M, Forsgren A, Hellsten S. The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*. 1984;18(1):37-42. doi:10.3109/00365598409182161

156. Grabe M, Forsgren A, Björk T, Hellsten S. Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. *Eur J Clin Microbiol*. 1987;6(1):11-17. doi:10.1007/BF02097183

157. Sayin Kutlu S, Aybek Z, Tekin K, et al. Is short course of antimicrobial therapy for asymptomatic bacteriuria before urologic surgical procedures sufficient? *J Infect Dev Ctries*. 2012;6(2):143-147. doi:10.3855/jidc.1781

158. Lightner DJ, Wymer K, Sanchez J, Kavoussi L. Best practice statement on urologic procedures and antimicrobial prophylaxis. *J Urol*. 2020;203(2):351-356. doi:10.1097/JU.0000000000000509

159. Moehring RW, Yarrington ME, Warren BG, et al; Centers for Disease Control and Prevention's Prevention Epicenters Program. Evaluation of an opt-out protocol for antibiotic de-escalation in patients with suspected sepsis: a multicenter, randomized, controlled trial. *Clin Infect Dis*. 2023;76(3):433-442. doi:10.1093/cid/ciac787

160. Leone M, Bechis C, Baumstarck K, et al; AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med*. 2014;40(10):1399-1408. doi:10.1007/s00134-014-3411-8

161. Chopra V, O'Horo JC, Rogers MAM, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2013;34(9):908-918. doi:10.1086/671737

162. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. *Am J Med*. 2012;125(8):733-741. doi:10.1016/j.amjmed.2012.04.010

163. Chopra V, Flanders SA, Saint S. The problem with peripherally inserted central catheters. *JAMA*. 2012;308(15):1527-1528. doi:10.1001/jama.2012.12704

164. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311-325. doi:10.1016/S0140-6736(13)60592-9

165. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177(9):1308-1315. doi:10.1001/jamainternmed.2017.1938

166. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036

167. Keller SC, Williams D, Gavgani M, et al. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2018;66(1):11-19. doi:10.1093/cid/cix733

168. Rieger KL, Bosso JA, MacVane SH, Temple Z, Wahlquist A, Bohm N. Intravenous-only or intravenous transitioned to oral antimicrobials for enterobacteriaceae-associated bacteremic urinary tract infection. *Pharmacotherapy*. 2017;37(11):1479-1483. doi:10.1002/phar.2024

169. Gamble KC, Rose DT, Sapozhnikov J. Intravenous to oral antibiotics versus intravenous antibiotics: a step-up or a step-down for extended spectrum β-lactamase (ESBL)-producing urinary tract infections without concomitant bacteraemia? *Int J Antimicrob Agents*. 2022;59(3):106541. doi:10.1016/j.ijantimicag.2022.106541

170. Mouwen AMA, Dijkstra JA, Jong E, Buijtels PCAM, Pasker-de Jong PCM, Nagtegaal JE. Early switching of antibiotic therapy from intravenous to oral using a combination of education, pocket-sized cards and switch advice: a practical intervention resulting in reduced length of hospital stay. *Int J Antimicrob Agents*. 2020;55(1):105769. doi:10.1016/j.ijantimicag.2019.07.020

171. Gandhi K, Wrzesinski M, Bunnell K, Gibble A. Oral antibiotic step-down therapy for nonstaphylococcal gram-positive bloodstream infections. *Diagn Microbiol Infect Dis*. 2023;107(4):116068. doi:10.1016/j.diagmicrobio.2023.116068

172. Olson J, Franz-O'Neal E, Cipriano FA, Ou Z, Presson AP, Thorell EA. Impact of early oral antibiotic therapy in infants with bacteremic urinary tract infections. *Hosp Pediatr*. 2022;12(7):632-638. doi:10.1542/hpeds.2021-006479

173. McAlister MJ, Rose DT, Hudson FP, Padilla-Tolentino E, Jaso TC. Oral β-lactams vs fluoroquinolones and trimethoprim/sulfamethoxazole for step-down therapy for Escherichia coli, Proteus mirabilis, and Klebsiella pneumoniae bacteremia. *Am J Health Syst Pharm*. 2023;80(suppl 1):S33-S41. doi:10.1093/ajhp/zxac202

174. Eron LJ, Passos S. Early discharge of infected patients through appropriate antibiotic use. *Arch Intern Med*. 2001;161(1):61-65. doi:10.1001/archinte.161.1.61

175. Khan DA, Banerji A, Blumenthal KG, et al; Chief Editor(s); Workgroup Contributors; Joint Task Force on Practice Parameters Reviewers. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol*. 2022;150(6):1333-1393. doi:10.1016/j.jaci.2022.08.028

176. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393(10167):183-198. doi:10.1016/S0140-6736(18)32218-9

177. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract*. 2018;6(3):1019-1027.e2. doi:10.1016/j.jaip.2017.08.006

178. Hayden DA, White BP, Neely S, Bennett KK. Impact of fluoroquinolone susceptibility suppression on discharge prescribing for acute uncomplicated cystitis. *Open Forum Infect Dis*. 2023;10(10):ofad459. doi:10.1093/ofid/ofad459

179. Langford BJ, Seah J, Chan A, Downing M, Johnstone J, Matukas LM. Antimicrobial stewardship in the microbiology laboratory: impact of selective susceptibility reporting on ciprofloxacin utilization and susceptibility of gram-negative isolates to ciprofloxacin in a hospital setting. *J Clin Microbiol*. 2016;54(9):2343-2347. doi:10.1128/JCM.00950-16

180. Langford BJ, Daneman N, Diong C, et al. Antibiotic susceptibility reporting and association with antibiotic prescribing: a cohort study. *Clin Microbiol Infect*. 2021;27(4):568-575. doi:10.1016/j.cmi.2020.10.001

181. Nicolle LE. Asymptomatic bacteriuria in the elderly. *Infect Dis Clin North Am*. 1997;11(3):647-662. doi:10.1016/S0891-5520(05)70378-0

182. Ariathianto Y. Asymptomatic bacteriuria—prevalence in the elderly population. *Aust Fam Physician*. 2011;40(10):805-809.

183. Lin YT, Chen LK, Lin MH, Hwang SJ. Asymptomatic bacteriuria among the institutionalized elderly. *J Chin Med Assoc*. 2006;69(5):213-217. doi:10.1016/S1726-4901(09)70221-7

184. Childs SJ, Egan RJ. Bacteriuria and urinary infections in the elderly. *Urol Clin North Am*. 1996;23(1):43-54. doi:10.1016/S0094-0143(05)70292-5

185. Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D. Epidemiology of bacteriuria in an elderly ambulatory population. *Am J Med*. 1986;80(2):208-214. doi:10.1016/0002-9343(86)90011-2

186. Boscia JA, Kobasa WD, Abrutyn E, Levison ME, Kaplan AM, Kaye D. Lack of association between bacteriuria and symptoms in the elderly. *Am J Med*. 1986;81(6):979-982. doi:10.1016/0002-9343(86)90391-8

187. Ostrow O, Prodanuk M, Foong Y, et al. Decreasing misdiagnoses of urinary tract infections in a pediatric emergency department. *Pediatrics*. 2022;150(1):e2021055866. doi:10.1542/peds.2021-055866

188. Choi DM, Heo TH, Yim HE, Yoo KH. Evaluation of new American Academy of Pediatrics guideline for febrile urinary tract infection. *Korean J Pediatr*. 2015;58(9):341-346. doi:10.3345/kjp.2015.58.9.341

189. Brandström P, Lindén M. How Swedish guidelines on urinary tract infections in children compare to Canadian, American and European guidelines. *Acta Paediatr*. 2021;110(6):1759-1771. doi:10.1111/apa.15727

190. 't Hoen LA, Bogaert G, Radmayr C, et al. Update of the EAU/ESPU guidelines on urinary tract infections in children. *J Pediatr Urol*. 2021;17(2):200-207. doi:10.1016/j.jpurol.2021.01.037

191. Azzarone G, Liewehr S, O'Connor K. Cystitis. *Pediatr Rev*. 2007;28(12):474-476. doi:10.1542/pir.28.12.474

192. Raszka WV Jr, Khan O. Pyelonephritis. *Pediatr Rev*. 2005;26(10):364-370. doi:10.1542/pir.26.10.364

193. SUBCOMMITTEE ON URINARY TRACT INFECTION. 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*. 2016;138(6):e20163026. doi:10.1542/peds.2016-3026

194. Tullus K, Shaikh N. Urinary tract infections in children. *Lancet*. 2020;395(10237):1659-1668. doi:10.1016/S0140-6736(20)30676-0

195. Karavanaki K, Koufadaki AM, Soldatou A, et al. Fever duration during treated urinary tract infections and development of permanent renal lesions. *Arch Dis Child*. 2019;104(5):466-470. doi:10.1136/archdischild-2017-314576

196. Massanyi EZ, Preece J, Gupta A, Lin SM, Wang MH. Utility of screening ultrasound after first febrile UTI among patients with clinically significant vesicoureteral reflux. *Urology*. 2013;82(4):905-909. doi:10.1016/j.urology.2013.04.026

197. Nelson CP, Johnson EK, Logvinenko T, Chow JS. Ultrasound as a screening test for genitourinary anomalies in children with UTI. *Pediatrics*. 2014;133(3):e394-e403. doi:10.1542/peds.2013-2109

198. Alon US, Ganapathy S. Should renal ultrasonography be done routinely in children with first urinary tract infection? *Clin Pediatr (Phila)*. 1999;38(1):21-25. doi:10.1177/000992289903800103

199. Shaikh N, Spingarn RB, Hum SW. Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. *Cochrane Database Syst Rev*. 2016;7(7):CD010657. doi:10.1002/14651858.CD010657.pub2

200. Jahnukainen T, Honkinen O, Ruuskanen O, Mertsola J. Ultrasonography after the first febrile urinary tract infection in children. *Eur J Pediatr*. 2006;165(8):556-559. doi:10.1007/s00431-006-0113-4

201. Battula V, Krupanandan RK, Nambi PS, Ramachandran B. Safety and feasibility of antibiotic de-escalation in critically ill children with sepsis—a prospective analytical study from a pediatric ICU. *Front Pediatr*. 2021;9:640857. doi:10.3389/fped.2021.640857

202. Ibrahim NA, Bakry MM, Ching SE, Tahir NM, Shah NN. Early empiric antibiotic de-escalation in suspected early onset neonatal sepsis. *Indian J Pharm Sci*. 2019;81(5):913-921. doi:10.36468/pharmaceutical-sciences.586

203. Antonio MEE, Cassandra BGC, Emiliano RJD, et al. Treatment of asymptomatic bacteriuria in the first 2 months after kidney transplant: a controlled clinical trial. *Transpl Infect Dis*. 2022;24(6):e13934. doi:10.1111/tid.13934

204. Alexopoulos E, Memmos D, Sakellariou G, Paschalidou E, Kyrou A, Papadimitriou M. Urinary tract infections after renal transplantation. *Drugs Exp Clin Res*. 1985;11(2):101-105.

205. Khosravi AD, Abasi Montazeri E, Ghorbani A, Parhizgari N. Bacterial urinary tract infection in renal transplant recipients and their antibiotic resistance pattern: a four-year study. *Iran J Microbiol*. 2014;6(2):74-78.

206. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13507. doi:10.1111/ctr.13507

207. Amano M, Shimizu T. Emphysematous cystitis: a review of the literature. *Intern Med*. 2014;53(2):79-82. doi:10.2169/internalmedicine.53.1121

208. Wu SY, Yang SSD, Chang SJ, Hsu CK. Emphysematous pyelonephritis: classification, management, and prognosis. *Tzu Chi Med J*. 2022;34(3):297-302. doi:10.4103/tcmj.tcmj_257_21

209. Somani BK, Nabi G, Thorpe P, Hussey J, Cook J, N'Dow J; ABACUS Research Group. Is percutaneous drainage the new gold standard in the management of emphysematous pyelonephritis: evidence from a systematic review. *J Urol*. 2008;179(5):1844-1849. doi:10.1016/j.juro.2008.01.019

210. Thomas AA, Lane BR, Thomas AZ, Remer EM, Campbell SC, Shoskes DA. Emphysematous cystitis: a review of 135 cases. *BJU Int*. 2007;100(1):17-20. doi:10.1111/j.1464-410X.2007.06930.x

211. Rubilotta E, Balzarro M, Lacola V, Sarti A, Porcaro AB, Artibani W. Current clinical management of renal and perinephric abscesses: a literature review. *Urologia*. 2014;81(3):144-147. doi:10.5301/urologia.5000044

212. Lee SH, Jung HJ, Mah SY, Chung BH. Renal abscesses measuring 5 cm or less: outcome of medical treatment without therapeutic drainage. *Yonsei Med J*. 2010;51(4):569-573. doi:10.3349/ymj.2010.51.4.569

213. Siegel JF, Smith A, Moldwin R. Minimally invasive treatment of renal abscess. *J Urol*. 1996;155(1):52-55. doi:10.1016/S0022-5347(01)66536-4

214. Coelho RF, Schneider-Monteiro ED, Mesquita JLB, Mazzucchi E, Marmo Lucon A, Srougi M. Renal and perinephric abscesses: analysis of 65 consecutive cases. *World J Surg*. 2007;31(2):431-436. doi:10.1007/s00268-006-0162-x

215. Shu T, Green JM, Orihuela E. Renal and perirenal abscesses in patients with otherwise anatomically normal urinary tracts. *J Urol*. 2004;172(1):148-150. doi:10.1097/01.ju.0000132140.48587.b8

216. Meng MV, Mario LA, McAninch JW. Current treatment and outcomes of perinephric abscesses. *J Urol*. 2002;168(4 Pt 1):1337-1340. doi:10.1016/S0022-5347(05)64443-6

217. Etienne M, Chavanet P, Sibert L, et al. Acute bacterial prostatitis: heterogeneity in diagnostic criteria and management: retrospective multicentric analysis of 371 patients diagnosed with acute prostatitis. *BMC Infect Dis*. 2008;8:12. doi:10.1186/1471-2334-8-12

218. McNaughton Collins M, Fowler FJ Jr, Elliott DB, Albertsen PC, Barry MJ. Diagnosing and treating chronic prostatitis: do urologists use the four-glass test? *Urology*. 2000;55(3):403-407. doi:10.1016/S0090-4295(99)00536-1

219. Gamé X, Vincendeau S, Palascak R, Milcent S, Fournier R, Houlgatte A. Total and free serum prostate specific antigen levels during the first month of acute prostatitis. *Eur Urol*. 2003;43(6):702-705. doi:10.1016/S0302-2838(03)00158-1

220. Gill BC, Shoskes DA. Bacterial prostatitis. *Curr Opin Infect Dis*. 2016;29(1):86-91. doi:10.1097/QCO.0000000000000222

221. Bradshaw AW, Pe M, Bechis SK, et al. Antibiotics are not necessary during routine cystoscopic stent removal: a randomized controlled trial at UC San Diego. *Urol Ann*. 2020;12(4):373-378. doi:10.4103/UA.UA_130_19

222. Westhoff N, Anokhin A, Patroi P, Neuberger M, Siegel F, Pfalzgraf D. Prospective evaluation of antibiotic management in ureteral stent and nephrostomy interventions. *Urol Int*. 2022;106(4):411-418. doi:10.1159/000517546

223. Bonkat G, Bartoletti R, Bruyere F. EAU Guidelines on Urological Infections 2022. Published online 2022. Accessed September 20, 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-Infections-2022.pdf

224. Yang C, Wei H, Zhan H, et al. Effect of preoperative prophylactic antibiotic use on postoperative infection after percutaneous nephrolithotomy in patients with negative urine culture: a single-center randomized controlled trial. *World J Urol*. 2023;41(12):3687-3693. doi:10.1007/s00345-023-04623-5

225. Darenkov AF, Derevianko II, Martov AG, Kotliarova GA, Kondrat'eva EM, Siniukhin VN. [The prevention of infectious-inflammatory complications in the postoperative period in percutaneous surgical interventions in patients with urolithiasis]. *Urol Nefrol (Mosk)*. 1994;(2):24-26.

226. Jung HD, Cho KS, Moon YJ, Chung DY, Kang DH, Lee JY. Antibiotic prophylaxis for percutaneous nephrolithotomy: an updated systematic review and meta-analysis. *PLoS One*. 2022;17(4):e0267233. doi:10.1371/journal.pone.0267233

227. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256. doi:10.1097/01.CCM.0000050454.01978.3B

228. Bag S, Kumar S, Taneja N, Sharma V, Mandal AK, Singh SK. One week of nitrofurantoin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *Urology*. 2011;77(1):45-49. doi:10.1016/j.urology.2010.03.025

229. Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *BJU Int*. 2006;98(5):1075-1079. doi:10.1111/j.1464-410X.2006.06450.x

230. Fisher JF, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infections–treatment. *Clin Infect Dis*. 2011;52(suppl 6):S457-S466. doi:10.1093/cid/cir112

231. Mathers MJ, Lazica DA, Roth S. [Non-bacterial cystitis: principles, diagnostics and etiogenic therapy options]. *Aktuelle Urol*. 2010;41(6):361-368. doi:10.1055/s-0030-1262615

232. Luciani LG, Mattevi D. Urinary tract infections: virus. *Encyclopedia Infection Immunity*. 2022;3:32-43. doi:10.1016/B978-0-12-818731-9.00139-7

233. Hirsch HH. BK virus: opportunity makes a pathogen. *Clin Infect Dis*. 2005;41(3):354-360. doi:10.1086/431488

234. Allen CW, Alexander SI. Adenovirus associated haematuria. *Arch Dis Child*. 2005;90(3):305-306. doi:10.1136/adc.2003.037952

235. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. *Nephrol Dial Transplant*. 2015;30(2):209-217. doi:10.1093/ndt/gfu023

236. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK polyomavirus: clinical aspects, immune regulation, and emerging therapies. *Clin Microbiol Rev*. 2017;30(2):503-528. doi:10.1128/CMR.00074-16

237. Krajewski W, Kamińska D, Poterek A, et al. Pathogenicity of BK virus on the urinary system. *Cent European J Urol*. 2020;73(1):94-103. doi:10.5173/ceju.2020.0034

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Supplemental Online Content

Nelson Z, Aslan AT, Beahm NP, et al. Guidelines for the prevention, diagnosis, and management of urinary tract infections in pediatrics and adults: a WikiGuidelines group consensus statement. *JAMA Netw Open*. 2024;7(11):e2444495. doi:10.1001/jamanetworkopen.2024.44495

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eAppendix 1: PROPHYLAXIS AND PREVENTION

Q1: What is the role of pharmacotherapy for the prevention of urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Pharmacotherapy can be considered for the prevention of urinary tract infections (UTIs) in women with recurrent UTIs. Postcoital administration of trimethoprim/sulfamethoxazole (TMP/SMX) or ciprofloxacin appears to reduce the incidence of UTIs in women compared to placebo.[1] No significant difference in effectiveness between intermittent, defined as the use of antibiotics after a trigger such as coitus, and continuous strategies has been demonstrated in high quality studies.[2] Benefits of antibiotic prophylaxis appear confined to their usage period and the optimal duration that balances individual and ecological risks with effectiveness are unclear. Observational data indicate that nitrofurantoin, norfloxacin, and TMP/SMX are comparatively effective, though conclusions are limited based on the study design.[3] There is limited and conflicting data on antibiotic prophylaxis for children.[4–6]

Overall Summary

The efficacy of postcoital TMP/SMX was evaluated against placebo in a cohort of non-pregnant women in 1990 by Stapleton et al.[1] Women who had experienced at least two culture-confirmed UTI in the previous year were recruited. The study involved 16 participants receiving TMP/SMX and 11 receiving a placebo, with similar self-reported sexual activity between groups. The results indicated a significant reduction in UTI occurrence in the TMP/SMX group, with only two infections compared to nine in the placebo group, equating to infection rates of 0.3 and 3.6 per patient-year, respectively. The authors concluded that postcoital TMP/SMX is highly effective for the prevention of recurrent UTIs in young women predisposed to frequent infections. A subsequent study in 1997 compared the effectiveness of post-coital versus daily ciprofloxacin prophylaxis over a 12-month period in 135 sexually active premenopausal women, followed by an observational year post-treatment.[2] Before the intervention, the groups experienced 3.67 and 3.74 UTIs per patient during the study period, respectively. The intervention revealed a substantial decrease in infection rates to 0.043 for post-coital prophylaxis and 0.031 for daily prophylaxis, which persisted following the cessation of treatment. Although not a non-inferiority design, the authors concluded that long-term post-coital prophylaxis with ciprofloxacin was as effective as daily prophylaxis in preventing UTIs and had the added benefit of reducing antibiotic exposure by approximately one-third.

Three randomized studies involving a total of 596 patients compared continuous antibiotic use with intermittent use following specific triggers such as after sexual intercourse ("post-coital"), or activities like micturition, diarrhea, constipation, travel, and long walks compared to continuous prophylaxis and once-a-week or once-a-month regimens, without linking to specific events.[2,7,8] No significant difference in effectiveness was found between continuous and intermittent antibiotic prophylaxis strategies. The benefits of antibiotics were mostly confined to their usage period, and the optimal duration for minimizing adverse effects without compromising efficacy is unclear.

Based on nine head-to-head studies including 636 patients (with available efficacy data), nitrofurantoin, norfloxacin, and TMP/SMX are similarly effective[9–17], although local resistance patterns may impact effectiveness. These findings align with a recent systematic review and meta-analysis of 23 RCTs found that antibiotic prophylaxis reduces the risk of UTIs compared to placebo with no significant difference in efficacy between different antibiotics.[3] This meta-analysis also showed that both intermittent and continuous strategies are equally effective. If pursuing an antimicrobial prophylaxis strategy, it may be important to choose a specific agent with consideration of the potential for individual and ecological collateral damage, patient allergies or intolerances, or contraindications.

Antibiotic prophylaxis for children is not routinely recommended due to limited and conflicting data.[4] A systematic review did not find sufficient evidence to recommended prophylaxis in children with prior UTIs, recurrent UTIs, vesicoureteral reflux (VUR), isolated hydronephrosis, or neurogenic bladder. Though it is sometimes considered in children with significant obstructive uropathies pending surgical correction, its overall role in preventing recurrences is limited, and it carries the risk of promoting antibiotic resistance.[5,6,18] A recent phase 3, multicenter, randomized trial in Europe found that continuous antibiotic prophylaxis in infants with vesicoureteral reflux had a small benefit in preventing a first symptomatic UTI, but did not reduce complications such as kidney scarring or affect kidney function. However, antibiotic resistance was more common in the prophylaxis group, and the results may not be generalizable to non-White infants or those with prior UTIs.[19]

Overall Conclusions

The decision to use antibiotic prophylaxis must balance the prevention of UTIs against the risk of adverse drug events, antimicrobial resistance, and microbiome disruption. Though these results are consistent across studies, these studies are small and of insufficient quality to provide a clear strong recommendation.

Q2: Is there a role for cranberry juice or supplements in the prevention of urinary tract infections?

Clear Recommendation

Executive Summary

Most prospective studies have indicated that cranberry products can reduce the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, children, and individuals susceptible to UTIs after interventions.[20–52] Evidence for their use in older adults, those with bladder emptying problems, or pregnant women is insufficient to make a clear recommendation for or against use.

Overall summary

A Cochrane review analyzed 50 RCTs with 8,857 participants and found that cranberry products can reduce the risk of symptomatic, culture-verified UTIs.[53] In this review, studies with the outcome of symptomatic, culture-verified UTIs, cranberry products reduced the risk of UTIs (6,211 participants: RR 0.70, 95% CI 0.58 to 0.84; $I^2 = 69\%$). This benefit was found in women with recurrent UTIs, children, and individuals susceptible to UTIs after interventions. However, there is no strong evidence to support their use in older adults (RR 0.93, 95% CI 0.67 to 1.30), those with bladder emptying problems (RR 0.97, 95% CI 0.78 to 1.19), or pregnant women (RR 1.06, 95% CI 0.75 to 1.50). Cranberry products were compared with probiotics in three studies, antibiotics in six studies, cranberry tablets with cranberry liquid in one study, and different doses of proanthocyanidins in two studies. There was no significant benefit of cranberry products compared to antibiotics. A reduction in UTIs was found compared to probiotics (RR 0.39, 95% CI 0.27 to 0.56). No clear differences in effectiveness between cranberry juice and tablets or among different doses of PACs was found. Gastrointestinal side effects were similar between cranberry and placebo groups.

Q3: Can water intake play a role in the prevention of urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

In one RCT that explored the effect of hydration on UTIs, increased water intake significantly reduced cystitis frequency in healthy women.[54] This RCT included 140 healthy women with recurrent cystitis, defined as 3 or more episodes in past year, who drank less than 1.5 liters of fluid per day. Participants were randomly assigned to either drink an additional 1.5 L of water daily or no additional fluids for 12 months. A quasi-experimental nursing home study was unable to demonstrate a benefit, but was under powered.[55] Beyond this single RCT, studies are limited and further research is needed to confirm these findings and explore this intervention in broader populations.

Overall Summary

Studies that aim to investigate the impact of hydration on uropathogenic bacterial activity have been reported.[56–58] In an RCT in which 140 healthy women with recurrent cystitis were randomized into drinking additional 1.5L of water daily in addition to usual fluid intake (water group) or no additional fluids (control group) for a total of 12 months, those in the additional water group had significantly decreased frequency of recurrent cystitis with mean (SD) number of cystitis episodes noted to be 1.7 (95% CI, 1.5-1.8) in the water group compared to 3.2 (95%

CI, 3.0-3.4) in the control group.[54] In a quasi-experimental study in which nursing home residents were randomly assigned to an 8-week hydration management intervention or to a control group, there were no UTIs in the treatment group and 1 in the control group. Due to small sample size, statistically significant differences were not demonstrated.[55]
Overall, water intake was shown to decrease UTIs in one RCT among healthy women. Further research is needed to confirm this effect and to explore other populations. Given the low risk nature of the intervention, pending a confirmatory study, it is reasonable to offer this intervention to healthy women with recurrent UTIs.

Q4: Is there a role for topical estrogen in the prevention of urinary tract infections?

Clear Recommendation

Executive Summary

Based on available evidence from thirty RCTs and one large retrospective observational study, topical estrogen is effective at reducing recurrent UTIs in post-menopausal women.[59] During peri-menopause loss of estrogen causes changes within the vaginal microbiome leading to loss of *Lactobacillus* species, an increase in vaginal pH, and an increased risk of UTIs.[60] The use of topical estrogen may help to reduce vaginal atrophy, restore the vaginal microbiome, and reduce the frequency of UTIs.[55] Recent evidence supports using vaginal estrogen therapy for breast cancer patients with genitourinary symptoms when nonhormonal treatments fail.[62] Topical estrogen is thought to have minimal systemic absorption and no concerning safety signals with regard to stroke, venous thromboembolism, invasive breast cancer, colorectal cancer, and endometrial cancer were been identified in a large prospective cohort study of over 45,000 women[63], it remains reasonable for biological females with a history of estrogen-related malignancies to discuss the risk and benefit of this treatment with their healthcare team prior to initiation.

Overall Summary

Estrogen has a significant effect on the vaginal microbiome by prompting the growth of *Lactobacillus* which produces lactic acid that lowers vaginal pH and consequently prevents growth of common genitourinary pathogens associated with UTIs. Post-menopausal females experience a loss of estrogen leading to a decrease of *Lactobacillus* in the vaginal microbiome.[55] Additionally, the loss of estrogen can lead to vaginal atrophy, which often mimics symptoms of UTIs.[60,64,65] Topical estrogen can be applied locally without systemic effects. Topical estrogen is available in three forms: topical cream, vaginal insert, and vaginal ring.[65] The role of topical estrogen in reducing episodes of recurrent UTIs in post-menopausal females has been evaluated in several studies.

A systematic review examined the relationship between menopause, urinary symptoms and the effects of hormone therapy on these symptoms in perimenopausal and postmenopausal women.[66] The review included 30 RCTs involving estrogen therapy and found insufficient evidence to confirm a direct association between menopause and urinary symptoms. However, the review did conclude systemic hormone therapy (HT) might cause or worsen urinary incontinence, while

vaginal estrogen therapy improves dysuria, frequency, urge and stress incontinence, and recurrent UTIs in menopausal women. Vaginal estrogen is beneficial for improving urinary symptoms and reducing the risk of recurrent UTIs in postmenopausal women. A study by Simunic et al with 1612 patients examined the efficacy of 25 microg of micronized 17beta-estradiol for urogenital complaints in a 12-month double-blind, placebo-controlled trial and showed that the estrogen group had an 85.5% success rate in symptom improvement compared to 41.4% in the placebo group.[61] Significant improvements were noted in urinary atrophy symptoms, cystometric capacity, and the volume at which urgency and desire to void were felt, alongside a decrease in uninhibited bladder contractions. Side effects were minimal (7.8%), and the treatment did not increase serum estrogen levels or stimulate endometrial growth, indicating that micronized 17beta-estradiol is an effective and safe treatment for urogenital complaints. Recent findings from a cohort study published in JAMA Oncology indicate no increased risk of early breast cancer-specific mortality in patients using vaginal estrogen therapy compared with those not using HRT. Based on this evidence, vaginal estrogen therapy can be considered for patients with breast cancer and genitourinary symptoms, particularly when nonhormonal treatments have been ineffective.[62] Additional safety data for vaginal estrogen was provided by a large prospective cohort study using data from participants of the Women's Health Initiative study.[63] The women included were aged 50 to 79 years old and did not use systemic estrogen therapy during follow-up (median: 7.2 years). Data was collected regarding incident coronary heart disease, invasive breast cancer, stroke, colorectal cancer, endometrial cancer, pulmonary embolism, and deep vein thromboses (collectively, venous thromboembolism). Hazard ratios derived from Cox proportional hazards were adjusted for age, education, past hormonal therapy use, history of cancer, history of cardiovascular disease, history of venous thromboembolism, race/ethnicity, BMI, diabetes, physical activity level, hypertension, Gail breast cancer risk score, previous fracture, smoking, household income, and alcohol intake. Among women with an intact uterus, risks of all of the aforementioned events were significantly lower in vaginal estrogen users compared with non-users (adjusted HR = 0.68, 95% CI: 0.55 to 0.86). Among patients with prior hysterectomy, the risks of each of the individual events and overall were not significantly different in users of vaginal estrogen compared with non-users (adjusted HR = 0.94, 95% CI: 0.7 to 1.26). The entire cohort, regardless of hysterectomy status, saw significantly lower risks for the aforementioned events (adjusted HR = 0.76, 95% CI: 0.64 to 0.91). These findings are consistent with other observational studies that suggest no association between vaginal estrogen use and an increased risk for breast cancer[67], endometrial cancer[68], hip fracture[69], venous thromboembolism[70], and/or coronary heart disease.[71]

Other RCTs have demonstrated that topical estrogen can reduce the frequency of recurrent UTI episodes in post-menopausal women. Raz et al were the first to conduct a randomized, double-blinded, placebo-controlled trial in the early 1990s that found patients receiving vaginal estrogen cream were significantly less likely to develop UTIs (0.5 vs 5.9 per patient, $P < 0.001$) corresponding to fewer mean antibiotic days (6.9 ± 1.1 vs 32 ± 7.8, $P < 0.001$).[72] The study enrolled 93 postmenopausal women with a history of recurrent UTI for a period of eight months. This study highlighted the relationship between estrogen and the vaginal microbiome as the cohort receiving topical estrogen demonstrated significant reductions in the vaginal pH after eight months of therapy. Similarly, a randomized, open-label, parallel group RCT also conducted in the 1990s **enrolled** a total of 108 women and randomly assigned 53 to the Estring group and 55 to the control group. The study found that patients who received estradiol vaginal ring therapy

were significantly more likely to remain UTI free (P=0.008).[73] Several years after their first RCT, Raz et al, conducted a second randomized, double-blind, double-dummy, control trial comparing estrogen-containing vaginal pessary , (n=86) to once daily nitrofurantoin for nine months (n=85).[61] Rates of symptomatic UTIs and asymptomatic bacteriuria (ASB) were much higher in the estrogen vaginal pessary cohort (85 UTIs and 39 ASB episodes vs 30 UTIs & 18 ASB episodes, P = 0.0003) and, unlike their previous study, the estrogen cohort did not show a significant decrease in vaginal pH nor an increase in *Lactobacillus* colonization.[59, 74] The authors hypothesized this difference was likely due to differences in the topical estrogen formulations used. The first study used an estrogen cream while the later study used an estrogen vaginal pessary as some women found the vaginal cream applicators difficult to use.[61]

In the last two decades, two additional RCTs were published to further define the relationship between topical estrogen and recurrent UTIs.[75,76] Dessole and colleagues enrolled postmenopausal symptomatic females in the early 2000s in a prospective, randomized, placebo-controlled trial to receive either vaginal estriol ovules or placebo vaginal suppositories, with 44 participants in each arm for a total duration of 6 months. While the primary outcome illustrated improvement in urinary incontinence and vaginal atrophy symptoms in patients receiving estrogen therapy (68% vs 16%, P <0.01), the study also demonstrated significant differences in bacteriuria and vaginal pH. Rates of ASB were similar at the beginning of the trial (17 cases in the estrogen arm vs 16 cases in the placebo arm) but differed significantly by the end of the six-month study period (6 cases vs 20 cases, P < 0.001). Likewise, the mean vaginal pH was also greatly influenced by vaginal estrogen therapy (4.12 $\pm$ 0.96 vs 5.30 $\pm$ 0.75, P < 0.05). [75] Lastly, the most recent multicenter, single-blinded, randomized placebo-controlled trial enrolled post-menopausal patients, or patients with prior hysterectomy experiencing menopausal symptoms for greater than one year, with a diagnosis of 3 ≥ UTIs within one year or at least 2 UTIs within six months. Patients were randomized 1:1:1 to receive vaginal cream, an estradiol ring, or placebo cream. Patients randomized to receive vaginal estrogen experienced significantly fewer UTIs by month six (50% [11/18] vs 95% [16/17], P=0.041) as defined by their intent-to-treat analysis.[76] However, this analysis combined the estrogen cream group (placebo controlled) with the open label vaginal ring group and this may have led to bias.

A multicenter retrospective review included 5,638 women prescribed vaginal estrogen for recurrent UTIs, defined as ≥ 3 urine cultures containing at least 1000 colony-forming units per milliliter of a uropathogen (with cultures separated by at least 14 days) in one year, between January 2009 and December 2019 within Kaiser Permanente Southern California healthcare system.[59] Approximately 93% of the women who filled a prescription for vaginal estrogen were post-menopausal, had a mean age of 70.4 ($\pm$ 11.92), and had an average baseline UTI frequency of 3.9 $\pm$ 1.3 episodes per year. Participants were followed for one year from the index pharmacy prescription fill, defined as the vaginal estrogen prescription filled post-UTI. The study was unable to report on concurrent UTI prevention techniques in addition to vaginal estrogen. Despite this, the study illustrated a 51.9% (1.8 $\pm$ 2.04; P <0.001) decrease in mean UTI frequency in the year following the index vaginal estrogen prescription. During the one-year study period, 55.3% of patients taking vaginal estrogen experienced ≤ 1 UTI with 31.4% having no UTIs as defined by urine cultures.

While several RCTs were identified, many limitations exist in these RCTs, most notably they were all small with populations ranging from 35 to 181 patients. While the level of evidence met our standard for a clear recommendation, we acknowledge that a large, high-quality, placebo RCT would be beneficial and could reach a different conclusion.

Overall summary

Several studies have demonstrated that topical estrogen may reduce episodes of recurrent UTIs in post-menopausal females. Topical estrogen is usually considered safe due to its localized, non-systemic effects.[65,70,77] However, it is prudent that clinicians considering topical estrogen should engage in shared decision making with their patients and weigh any real or perceived risks and benefits of therapy. For example, due to a lack of robust clinical evidence, it is rational that females with a history of estrogen-related malignancies speak to their healthcare professional prior to initiating topical estrogen treatment.[77]

Q5: Is there a role for methenamine hippurate in the prevention of urinary tract infections?

Clear recommendation

Executive Summary

Methenamine, approved in 1967 for recurrent UTI prophylaxis in those 12 and older, works by releasing formaldehyde in acidic urine, reducing bacterial resistance concerns. A systematic review that included a multicenter, open-label, randomized non-inferiority trial conducted in the United Kingdom from June 2016 to June 2018 compared the efficacy of methenamine with daily low-dose antibiotics in preventing recurrent UTIs in women aged 18 and older and found that methenamine was non-inferior to antibiotics for the prevention of UTIs.[78] Similarly, a non-blinded RCT compared methenamine with trimethoprim for preventing recurrent UTIs over a 12 month timeframe in adult women found non-inferiority for methenamine, with no significant difference in UTI recurrence rates between the two groups and similar adverse effects.[79] Therefore, we recommend the use of methenamine as an alternative to prophylactic antibiotics in patients with intact bladder anatomy.

Overall Summary

Methenamine, a non-antimicrobial medication that exerts its action by converting ammonia and formaldehyde in an acidic environment, was the first and only product approved for the prophylaxis of recurrent UTI in patients 12 years and older in 1967. Formaldehyde denatures proteins and nucleic acids of bacteria in a non-specific matter, therefore, there is no concern for bacterial resistance.[80] A systematic review conducted in 2023 following PRISMA guidelines, used PubMed, Embase, and the Cochrane library to identify studies on methenamine for UTI prophylaxis, including RCTs, case-control studies, and meta-analyses up to June 2023.[81] Eleven articles met the inclusion criteria, including one RCT, one non-inferiority trial and a case control study. Studies that did not primarily evaluate methenamine or studies combining methenamine

with another agent were excluded. In this review, methenamine was found to be effective and well-tolerated as an antibiotic-sparing option for UTI prophylaxis. Vitamin C is sometimes used with methenamine to enhance its effectiveness as a urinary antiseptic by acidifying the urine, which promotes the conversion of methenamine into formaldehyde, an antibacterial agent. However, clinical evidence supporting the routine use of vitamin C for this purpose is limited. Additionally, these supplements may increase gastrointestinal side effects in patients.[82]

Notably, a large, randomized, pragmatic trial in a routine NHS setting has shown that methenamine hippurate is non-inferior to current standard care (daily low-dose antibiotics) in preventing recurrent UTI in women[83]. The study included 240 women randomized to either methenamine hippurate or low-dose antibiotics for UTI prevention for a total of 12 months, with crossover allowed. Antibiotic-treated UTIs decreased in both groups, with methenamine hippurate showing 1.38 (95% confidence interval 1.05 to 1.72 episodes per person-year) episodes per person-year and antibiotics showing 0.89 episodes per person-year (95% confidence interval 0.65 to 1.12 episodes per person-year), confirming non-inferiority (absolute difference 0.49; 90% confidence interval 0.15 to 0.84). Methenamine hippurate was also found to be less costly and more effective in quality-adjusted life-years gained, though this was not consistent long-term. Higher antibiotic resistance was observed in the antibiotic group during treatment, while post-treatment, the methenamine hippurate group had a higher proportion of multi-drug resistant (MDR) *E. coli*.

A non-blinded RCT by Botros et al compared methenamine hippurate with trimethoprim for preventing recurrent UTIs over 12 months in women aged over 18.[79] Ninety-two patients were randomized to receive daily prophylaxis, and analyses showed no significant difference in UTI recurrence rates between the two groups, both having a 65% recurrence rate. The study concluded that methenamine hippurate was an effective alternative to trimethoprim for preventing recurrent UTIs, with similar recurrence rates and adverse effects.

Based on these consistent results in RCTs, we recommend the use of methenamine for prophylaxis of UTIs as an alternative to prophylactic antibiotics in patients with intact bladder anatomy.

Q6: Are probiotics effective in the prevention of urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

There is inconclusive evidence to recommend for or against the use of oral or vaginal probiotics to prevent urinary tract infections. Studies were heterogeneous as it pertains to the patient populations (children, premenopausal women, postmenopausal women, complicated UTI in patients with comorbidities), specific probiotics, route of administration, and study design.[84–87]

Overall Summary

Oral probiotics have been proposed as an alternative to long-term antibiotic prophylaxis to prevent recurrent urinary tract infections. Some researchers have proposed that probiotics do not exert a selective pressure on antimicrobial-resistant pathogens, thereby reducing colonization of the urinary tract by uropathogenic bacteria.[84,85,88] However, an RCT published by Wolff et al in 2019 demonstrated no change in the ratio of uropathogens and *Lactobacilli* in young healthy women taking probiotics[84]. Other proponents cite that probiotics have few side effects. Nevertheless, when studied for other conditions, the use of probiotics has been associated with bacteremia.[89] Furthermore, probiotics can be costly and may not be accessible to all patients.

Previously conducted Cochrane systematic reviews yielded inconclusive results regarding the efficacy of probiotics in preventing UTIs in adults and children and in patients with neuropathic bladder. [85,88] Study populations ranged from preterm infants, pre- and postmenopausal women, to patients with neurogenic bladder. The format of the studies also varied substantially. In some studies, probiotics were administered orally, whereas in other trials, they prescribed as vaginal suppositories, or intravesically. In addition, probiotics in some studies were either defined as one strain alone or a combination of several strains (e.g., *Lactobacillus rhamnosus* [GG]*, L. reuteri., L. crispatus, Bifidobacterium bifidum, B. lactis, Saccharomyces boulardii*). The variability in study designs and heterogeneity in outcomes are poorly amenable to meta-analysis.

The results of RCTs across diverse populations also have mixed results. Beerepoot et al. failed to demonstrate the non-inferiority of *L. rhamnosus* and *L. reuteri* capsules compared to standard treatment in postmenopausal women, although they noted reduced antimicrobial resistance.[90] Stapleton et al. observed a numerical reduction in UTI rates with L. crispatus vaginal suppositories in premenopausal women and increased vaginal colonization with the probiotic.[91] However, these findings did not reach statistical significance. Toh et al.'s trial, including spinal cord injury patients, showed no significant benefit from various oral probiotics compared to placebo.[86] In pediatric research, Sadeghi-Bojd et al. found that a probiotic blend significantly increased UTI-free survival in children aged 4 months to 5 years.[92] An RCT with preterm infants given *L. rhamnosus* (GG) saw a non-significant decrease in UTI occurrence.[93] Lastly, Quattrone et al. reported that *D*-mannose and *S. boulardii* administered orally around cystoscopy procedures resulted in lower rates of positive urinary cultures.[94]

Overall, currently available data do not support a role of probiotics for the prevention of UTIs outside the conduct of an adequately powered RCT.

Q7: Is there a role for *D*-mannose in the prevention of urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Despite biological plausibility for effectiveness[95], there is currently insufficient evidence to support or refute the use of *D*-mannose for the prevention of UTIs. Only 3 RCTs[96–98], one small open-label prospective cohort study[99], and a sub-group of another prospective cohort study[100] evaluated *D*-mannose alone for only prevention (not treatment) of UTIs. Discordant or uncertain results among the prospective studies along with small sample sizes and heterogeneity of specific

D-mannose regimens, study populations, comparators, UTI definitions, potential for reporting bias, and follow-up periods preclude a clear recommendation for or against its use. Adverse effects were seemingly infrequent although poorly reported, most of which included gastrointestinal symptoms and vaginal burning.[98,101,102]

Overall Summary

D-mannose is a naturally occurring monosaccharide which is theorized to competitively inhibit bacterial adherence to uroepithelial cells in the bladder wall.[95] As a result of this urothelial barrier mechanism, bacteria are proposed to bind to *D*-mannose and are expected to be excreted in the urine rather than invading the urothelium. *D*-mannose is neither bacteriostatic nor bactericidal, does not interfere with antibiotic activity, and reportedly has few side effects.[95]Target populations in which *D*-mannose has been investigated include premenopausal and postmenopausal women, men, post-urologic procedures, catheterized patients, among others. Patients with chronic kidney disease, stones, upper urinary tract infection (e.g., pyelonephritis), sepsis, interstitial cystitis, diabetes mellitus, and pregnant or breastfeeding patients have been consistently excluded from the studies.[95,98,101,102]

Most recently, a multicenter, double-blind, placebo-controlled randomized control trial published by Hayward et al (2024) evaluated the effectiveness of *D*-mannose in prevention of UTI in women with recurrent UTI (median number of episodes in the last 12 months = 4 [IQR: 1 to 10]) presenting to any of 99 primary care clinics in the United Kingdom.[98] This study enrolled nearly 600 women, the largest patient population of any study found in our review, who received 2 grams *D*-mannose powder daily (n = 303) versus a similar-volume scoop of fructose powder as placebo (n = 295). The primary outcome of interest was the proportion of women experiencing at least 1 further episode of clinically suspected UTI for which they contacted ambulatory care within 6 months of randomization established via primary care record review. Of the 294 women in the *D*-mannose group and 289 in the placebo group, 150 (51%) and 161 (55.7%) had a further episode of clinically suspected UTI respectively (RD = -4.7%; 95% CI: -13 to 3%). The proportion was noted to be similar in sensitivity and subgroup analyses, including a per protocol analysis and stratified analyses based on menopausal status, frequency of prior UTIs, symptom burden, time to next UTI, number of UTIs, antibiotic use, hospitalizations, and serious adverse events. The patient advisory panel suggested that to commit to daily use of a prophylactic regime, they would expect evidence of at least a 50% reduction in the chance of a further UTI episode during the period of prophylaxis. The power calculation was based on this assumption; thus, the study may not have been adequately powered to detect a smaller difference and the reasoning behind this decided clinical importance threshold could be debated. The authors of the study concluded that since the lower bound of the 95% CI did not eclipse -50%, *D*-mannose should not be recommended to prevent future episodes of UTI in women with a history of recurrent UTI in primary care.

Two systematic reviews and/or meta-analyses have been published[101,102]. A Cochrane systematic review published in 2022 evaluated the use of *D*-mannose for prevention and treatment of recurrent UTI.[101] Amongst the included studies (7 RCTs, totaling 719 participants), only 2 RCTs[96,97] compared *D*-mannose alone to either placebo or an antimicrobial prophylaxis option, totaling 411 patients total. No studies were comparable by dose or treatment

to enter into a meta-analysis by Cochrane standards. The two notable RCTs from this review are summarized below:

Kranjcec et al (2014) conducted a prospective randomized controlled trial to test the efficacy of *D*-mannose after initial antibiotic treatment of acute cystitis in preventing recurrent UTI in adult women (total in analysis = 308 women) with a history of recurrent UTI (median number of cystitis episodes in the last 6 months = 2) and no other significant comorbidities.[97] In this study, *D*-mannose (at a dose of 2 grams powder in 200 mL of water daily for 6 months) was compared to nitrofurantoin (50 mg nitrofurantoin daily for 6 months) and to no prophylaxis. Patients in the *D*-mannose group had a significantly lower risk of recurrent cystitis episode during prophylactic therapy compared to patients in the no prophylaxis group (RR = 0.24; 95% CI: 0.15 to 0.39). The difference in recurrent UTI episodes while on prophylaxis between the *D*-mannose and nitrofurantoin groups was not significant (14.6% in the *D*-mannose group vs. 20.4% in the nitrofurantoin group; RD = 5.8%). Patients who received *D*-mannose had much lower rates of side effects compared to nitrofurantoin (RR = 0.28; 95% CI: 0.13 to 0.57), although authors note the clinical importance of this is low as both were well tolerated. In this RCT, *D*-mannose appeared to be similarly efficacious to antimicrobial prophylaxis (with nitrofurantoin) and more effective than no prophylaxis when it came to preventing recurrent UTI episodes.

Porru et al (2014) conducted a randomized cross-over trial in non-pregnant women over 18 years old with acute symptomatic cystitis with a history of 3 or more UTI episodes with a positive urine culture in the preceding 12 months.[96] Patients were excluded if they had signs of upper tract or systemic disease (fever, flank pain, lumbar pain, CVA tenderness) or if they had pre-existing renal disease, anatomical abnormalities, a history of gynecological surgery or immunosuppressive medications or diseases. Patients (total in analysis = 60 women) were randomized to receive either *D*-mannose (1 gram three times daily for 2 weeks then twice daily for a total of 6 months) or to trimethoprim/sulfamethoxazole (160 mg TMP twice daily for 5 days for treatment followed by 160 mg TMP once daily for 1 week each month for 6 months total duration including treatment). At the 6-month time point, patients crossed over to the other group for an additional 6 months. The primary endpoint was average time to UTI recurrence. Average time to UTI recurrence was statistically longer in the *D*-mannose group as opposed to the antibiotic treatment group (200 days vs. 52.7 day, respectively; $p < 0.0001$). Twelve of the 60 patients had a positive urine culture during treatment/prophylaxis with *D*-mannose, though it is unclear how many of them had subsequent symptomatic UTIs.

Two other prospective studies have evaluated *D*-mannose alone as prophylaxis and/or treatment and were included in a prior systematic review and meta-analysis published in 2020.[102] These studies are reviewed below:

Domenici et al (2016) conducted a small (total n = 43) single center, prospective cohort study in women between 18 and 65 years old with acute cystitis or asymptomatic bacteriuria with ≥ 10^3 CFU/mL in a clean voided midstream urine sample.[100] These women had an average of 2.3 cystitis episodes in the last 6 months. All participants received *D*-mannose 1.5 grams twice daily for 3 days, then daily for 10 days as treatment, then either received *D*-mannose 1.5 grams daily for one week every other month for a total of 6 months (n = 22) or no prophylaxis (n = 21). Of those treated with D-mannose as prophylaxis for 6 months, only 1 of 22 (4.5%) patients had a

recurrence within that time frame compared with 7 of 21 (33.3%; $p = 0.05$). The small sample size clearly limits the generalizability of this study.

Phe et al. (2017) conducted a small (total n = 22) single-center, open-label, prospective feasibility study to evaluate *D*-mannose (dosed as 1.5 grams powder twice daily for 16 weeks) in preventing UTI in men (4 of 22) and women (18 of 22) with multiple sclerosis, 45% (10 of 22) of whom utilized chronic, indwelling urinary catheters.[99] Overall, 61 episodes of possible UTI were recorded based on signs and symptoms; 19 of those 61 possible episodes resulted in a positive urine culture. The number of monthly proven UTIs significantly decreased in patients with and without indwelling catheters. In the 10 patients without catheters, the number of UTIs per month decreased from 0.5 to 0.1 UTIs per month. In the 12 patients with catheters, the number of UTIs per month decreased from 0.7 to 0.2 UTIs per month. The median number of antibiotic prescriptions in the patients without catheters in the 16 weeks of treatment/prophylaxis was 1 (IQR: 0 to 2.2). The median number of antibiotic prescriptions in patients with catheters during the 16 weeks of *D*-mannose therapy was 2 (IQR: 0 to 3). At the end of the study 18 of 22 patients expressed a desire to continue to take *D*-mannose. The small sample size with no comparator clearly limits the generalizability of this study.

In all other evaluable studies found, *D*-mannose was combined with one or more other substances. For example, Lenger et al (2023) conducted a randomized control trial comparing *D*-mannose (2 grams per day) plus vaginal estrogen versus vaginal estrogen alone for prevention of recurrent urinary tract infections in postmenopausal women.[103] The study was terminated early as the futility analysis suggested the study lacked power – only 32 of the 71 eligible patients completed the study. Additionally, Quattrone et al (2023) evaluated *D*-mannose plus *Saccharomyces boulardii* in prevention of UTI and discomfort in patients undergoing cystoscopy for evaluation of bladder cancer.[94] Patients were randomized to receive *D*-mannose plus *S. boulardii* (3 billion CFU) every 12 hours for 6 days after cystoscopy vs. no treatment after cystoscopy. Discomfort and quality of life questionnaires were administered before and after the cystoscopy (7 days). 32 patients were enrolled (16 in each group). 3 patients (p=0.044) in the no treatment group had symptoms and positive urine cultures 7 days post- procedure. Discomfort and pain scores were less in the treatment group (statistically significant) than in the no treatment group, but there was no statistically significant difference in quality-of-life scores in the questionnaires.

Overall Conclusion

The conflicting nature and quality of existing prospective studies preclude a clear recommendation for or against the use of *D*-mannose for the prevention of future episodes of UTI in patients with a history of recurrent UTI.

eAppendix 2: DIAGNOSIS AND DIAGNOSTIC STEWARDSHIP

Q8: What are the clinical definitions of cystitis, complicated urinary tract infections, and pyelonephritis?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Cystitis and pyelonephritis are classically diagnosed clinically through signs and symptoms with evidence of inflammation (pyuria) and the presence of pathogenic bacteria in the urine. Typical nomenclature includes the use of terms such as cystitis, uncomplicated UTI, complicated UTI, and pyelonephritis. Cystitis, an inflammation of the bladder often indicated by dysuria, urgency, and suprapubic pain, is typically described not to show systemic infection signs like fever. Unfortunately, complicated UTI lacks a standard clinical definition due to diverse criteria in literature and guidelines. Complicated UTIs may involve catheters or other foreign bodies, complicating factors like structural anomalies or immunosuppression, or systemic symptoms. Pyelonephritis, kidney inflammation due to infection, includes systemic signs such as flank pain and fever, with or without cystitis symptoms. More precise clinical definitions, based on clinical studies linked to outcomes, are needed. Most WikiGuidelines authors strongly encourage the use of more precise descriptions of UTI in clinical practice rather than continuing to use vague terms such as “complicated” or “uncomplicated.”

Overall Summary

UTIs include cystitis and pyelonephritis and may present with numerous combinations of signs and symptoms. UTI is a clinical diagnosis, requiring the presence of clinical signs and symptoms of infection in the setting of inflammation (pyuria) and pathogenic bacteriuria in most patients. UTIs can be further classified as complicated; however, there is no uniformly accepted clinical definition. Based on the substantial heterogeneity in the clinical criteria used in existing literature and clinical practice guidelines, we cannot clearly recommend a *single* clinical definition to define complicated UTI. Most WikiGuidelines authors strongly encourage more precise descriptions of UTI where possible, rather than continuing to use more vague terms such as “complicated” or “uncomplicated.”

Cystitis

Cystitis is inflammation of the bladder, which in the context of a UTI would be caused by infection. Classic symptoms include dysuria and urinary urgency, frequency, and suprapubic and/or lower abdominal pain. Gross hematuria without other causes may occasionally be a sign of cystitis as well. It is generally believed that cystitis alone does not typically present with systemic signs and symptoms of infection. There is no minimum number of symptoms that clearly defines the presence of cystitis due to infection.[104]

There are non-infectious causes of cystitis and cystitis symptoms that clinicians should be aware of and explore if clinically suspected. Non-infectious causes include but are not limited to atrophic vaginitis, interstitial cystitis, drug induced cystitis, urinary retention, and/or urethral strictures. There are also infectious mimics which can be considered including urethritis, prostatitis, and pelvic inflammatory disease.

Complicated UTI

The definition of complicated UTI used in available literature is extremely diverse. How one defines "complicated" may be reflective of the patient's risk for treatment failure, the anatomical location of the infection, or the severity of infection, among other factors.[104] UTI's may be considered complicated, with or without the presence of pyelonephritis, based on the presence of an indwelling urinary catheter or other foreign body, systemic signs and symptoms of infection suggesting the infection extends outside of the lower urinary tract, or complicating host factors such as structural or functional urological abnormalities, immunosuppression, or comorbidities. Historically, male sex was considered a qualifying characteristic of complicated UTI, although not all clinicians accept this premise, and no data are available to support it outside the context of prostate infections, which one could reasonably argue should just be called "prostatitis".

Pyelonephritis

Pyelonephritis is inflammation of the kidneys due to infection and is often considered a subset of complicated UTIs. Signs and symptoms of pyelonephritis may include cystitis symptoms plus symptoms including fever, chills, and flank pain; signs including costovertebral angle (CVA) tenderness; and features of systemic illness including fever, tachycardia, hypotension, and/or leukocytosis.[104] False localizing symptoms like nausea and vomiting can also commonly occur.

Importance of Symptoms

The primary purpose of requiring the presence of symptoms and/or signs of UTI at the time of clinical diagnosis is often to differentiate infection from asymptomatic bacteriuria (ASB) or contamination and to help determine the need for antimicrobial treatment. Unfortunately, signs and symptoms of UTI may overlap with non-infectious syndromes. Therefore, it is reasonable to consider requiring the presence of more than one clinical symptom when ordering a diagnostic test and defining a UTI in the setting of positive tests.

For the purposes of RCTs and drug approvals, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) require a minimum number of symptoms consistent with UTI as outlined in their drug industry development and approval guidance documents (Table 1).[105]

The 2005 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Management of ASB defined acute uncomplicated UTI, acute nonobstructive pyelonephritis, and complicated UTI for the purposes of ruling out symptoms in the presence of bacteriuria.[106] The 2019 updated guidance uses the terms "local genitourinary symptoms", "classic urinary symptoms" and "systemic signs of infection (e.g., fever or hemodynamic instability) when defining lack of symptoms in patients with ASB.[107] The 2010 International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women by the IDSA and the European Society for Microbiology and Infectious Diseases (ESCMID) do not provide a clinical definition of acute uncomplicated cystitis or pyelonephritis.[104] Table 2 compares these definitions.[104,107–109]

UTI Definitions in Clinical Studies and Guidelines

Based on available data from clinical practice guidelines and RCTs that evaluated the use of antimicrobials for the treatment of UTI, there is no standard clinical definition of UTI used. A recent and comprehensive systematic review by Bilsen and colleagues effectively highlighted the heterogeneity in UTI definitions that are used in current research.[105] Among the 47 studies included in the review, 31 studies investigated the use of antimicrobials for the treatment of UTI (the remaining studies evaluated prophylactic antimicrobials). We identified 6 additional studies evaluating the use antimicrobials for the treatment of UTI using the same search strategy as Bilsen et al. that were published after the completion of their systematic review.[110–115] Among the total 37 studies, the clinical criteria used to define UTI varied considerably. Although most studies (n = 32, 86%) required the presence of clinical signs/symptoms, the type and number of symptoms varied and some studies did not explicitly specify which signs/symptoms were present (Table 3). While the clinical manifestations associated with cystitis and pyelonephritis are well described in the literature, there is a lack of consistency and consensus on the criteria used to define complicated UTI. Pyelonephritis may reasonably be considered a subset of complicated UTI or may be defined separately.

Purpose and significance of classifying UTIs as complicated or uncomplicated

Guidelines often categorize UTIs as uncomplicated or complicated, which is historically based on certain risk factors linked to severe outcomes, recurrence, relapse.[108] Definitions vary, but a complicated UTI is generally defined in a patient with an underlying functionally or structurally abnormal urinary tract. Uncomplicated UTIs have been reserved for premenopausal or nonpregnant women with no known urological abnormalities or comorbidities, which encompasses both uncomplicated cystitis and pyelonephritis.[104] Uncomplicated UTIs have also been microbiologically restricted to a few enteric pathogens with predictable antimicrobial resistance.[116] Regardless of how complicated UTIs are defined, the rationale has been that patients with complicated UTIs warrant more prudent management than those with uncomplicated ones. This typically includes a more comprehensive diagnostic investigation, longer treatment duration, higher dosing, and/or broader antibiotic coverage.[108,117] However, this classification has been conventionally established without high-quality supporting evidence and the definitions of both uncomplicated and complicated UTI have differed and evolved as discussed in eAppendix 2, Question 1.

More recently, the Infectious Disease Society of America (IDSA) has proposed more tailored definitions for complicated and uncomplicated UTIs, with an approach to treatment based on the extent of infection and the severity of illness.[118] Complicated UTIs are defined to include the possibility of extension beyond the bladder. Clinically, this is defined as a UTI with systematic symptoms, such as fever, or documented pyelonephritis or bacteremia. When neither of these stipulations are present, the UTI is to be considered acute simple cystitis.[118] Contrary to historic guidelines, IDSA proposed that a complicated UTI does not require the presence of underlying urologic abnormalities or severe comorbidities (including immunosuppression, advanced HIV infection, poorly controlled diabetes, etc.). This only applies to asymptomatic patients, as any systemic symptoms puts patients at a higher risk for more serious infection. Since this patient group has not traditionally been included in studies evaluating antibiotic regimens, they should be monitored closely with low threshold to initiate therapy to prevent a systemic infection. IDSA

proposes that all pyelonephritis should be considered a complicated UTI. Pregnant women and renal transplant recipients were excluded from this categorization.

Complicated UTIs are a highly heterogeneous group. Since IDSA's publication, new evidence is emerging and challenging the conception of this definition, specifically that UTIs in males are automatically considered complicated and require extended antibiotic treatments (over 10-14 days). Newer RCT evidence demonstrate that antibiotic courses less than 10-14 days are still effective in male UTIs.[114,119–122] While a retrospective outpatient study supported the absence of clinical benefit to treating male UTIs longer than seven days.[123] A recent meta-analysis demonstrated the clinical cure rate for complicated UTIs with novel antibiotics (ceftazidime/avibactam, plazomicin, etc.) was superior to conventional ones (piperacillin/tazobactam, ciprofloxacin, levofloxacin, etc.).[117]

Overall Conclusion

Overall, while the classification of UTIs as complicated or uncomplicated may be valuable in clinical practice, it is important to recognize that regardless of source, these definitions are generally not based on reproducible, high quality data. More research is required to definitively define these groups.

Table 1. Clinical criteria recommended by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for inclusion in UTI clinical studies		
	FDA	**EMA**
Complicated UTI and acute pyelonephritis	≥2 signs or symptoms: - chills or rigors or *warmth* associated with fever (e.g., oral temp > 38° C) - flank pain(pyelonephritis) - pelvic pain (cUTI) - CVA tenderness - dysuria, frequency, or urgency - nausea or vomiting Complicating factors: ≥ 1 of the following: - Functional or anatomical abnormality of the urinary tract - Urinary catheter **Exclusions**: - Ileal loops - Vesico-ureteral reflux - Suspected or confirmed prostatitis - Renal transplantation - Recent trauma/surgery to pelvis or urinary tract	Minimum number of signs/symptoms: - flank or pelvic pain - CVA tenderness - dysuria, frequency, or urgency Complicating factors: ≥1 of the following: - Indwelling urethral catheter - Urinary retention - Urinary obstruction - Neurogenic bladder **Exclusions**: - Ileal loops - Vesico-ureteric reflux - Signs/symptoms suggesting prostatitis
Uncomplicated UTI	≥2 signs or symptoms in <u>female</u> patients limited to: - Dysuria - Urinary frequency - Urinary urgency - Suprapubic pain	Minimum number of symptoms such as frequency, urgency, dysuria in female patients

Table 2. Clinical practice guideline definitions of UTI symptoms				
	Proposed IDSA[118]	**IDSA[105]**	**EUA[105]**	**AUA/CUA/SUFU[109]**
Complicated UTI and acute pyelonephritis	- Any infection beyond the bladder - Includes pyelonephritis, CAUTI, febrile or bacteremic patients	- Urinary symptoms plus functional or structural abnormalities of the urinary tract - CVA pain and tendernsess, often with fever (pyelonephritis)	- Dysuria, urgency, frequency, flank pain, CVA tenderness, suprapubic pain, fever, chills, nausea, vomiting - Anatomical or functional abnormalities of the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction - Presence of diabetes or immunosuppression	- Anatomical or functional abnormality of the urinary tract (e.g., stone disease, diverticulum, neurogenic bladder) - Immunocompromised host - Multi-drug resistant bacteria
Uncomplicated UTI	- All other infections not defined as complicated	- Frequency, urgency, dysuria, or suprapubic pain in a woman with a normal genitourinary tract	- Dysuria, frequency and urgency and the absence of vaginal discharge - Limited to non-pregnant women with no known relevant anatomical and functional abnormalities or comorbidities	- Dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, or new or worsening incontinence - Female host - No known factors that would increase susceptibility to develop UTI

Table 3. Specific signs and symptoms included in patient eligibility criteria from clinical studies. Table adapted from Bilsen et al.[124](2023) and updated with more recent data from clinical studies evaluating the treatment of UTI.

Symptoms/Signs	Acute cystitis (n=12)	Acute pyelonephritis[a] (n=19)	Complicated UTI Uncomplicated UTI Unspecified UTI(n=19)
Dysuria	9 (75)	10 (53)	15 (79)
Urgency	9 (75)	8 (42)	13 (68)
Frequency	9 (75)	9 (47)	12 63)
Suprapubic pain	5 (42)	0	10 (53)
Macroscopic hematuria	4 (33)	0	6 (32)
Lower abdominal pain	2 (17)	0	3 (16)
Perineal/prostate pain	1 (8)	0	3 (16)
Pelvic pain	0	2 (11)	3 (16)
Flank pain or CVA tenderness	1 (8)	15 (79)	5 (26)
New urinary incontinence	0	0	1 (5)
Worsening incontinence	0	0	1 (5)
Fevers	0	14 (74)	7 (37)
Chills or rigors	0	9	2 (11)
Nausea or vomiting	0	10 (53)	3 (16)
Symptoms not specified	3 (25)	4 (21)	2 (11)

[a]Data presented as N(%). Other symptoms mentioned in non-pyelonephritis studies: malodorous/cloudy urine (n=2), general weakness (n=1), vesical tenesmus (n=1), hypogastric pain (n=1), and nocturia (n=1). Additional criteria for the definition of acute pyelonephritis: elevated serum inflammatory parameters (n=1), signs on ultrasound or computed tomography (n=1), and hypotension (n=1)

Q9: What is the role and the sensitivity and specificity of a urinalysis for the diagnosis of urinary tract infections and when should clinicians order urine cultures?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)
Executive Summary

A complete urinalysis (UA) encompasses physical, chemical, and microscopic evaluations designed to aid in diagnosing renal, metabolic, oncologic, and infectious disorders. Unfortunately, the diagnostic value of UA for urinary tract infection is limited.[125,126] While the absence of pyuria can help rule out infection in most patient populations, the positive predictive value of pyuria for diagnosing infection is exceedingly low as it often indicates the presence of genitourinary inflammation due to many other possible non-infectious reasons (Table 4). For these reasons, WikiGuidelines authors suggest that UTI diagnosis should integrate clinical symptoms with UA findings and not rely on the test alone. Urine cultures are reasonable for complicated cases and/or recurrent UTIs, particularly in suspected pyelonephritis, to guide targeted therapy. In simple uncomplicated cystitis in healthy non-pregnant patients, routine cultures are not necessary.[18,127]

Overall Summary

Among the different components of UA, leukocyte esterase and nitrite tests are part of the chemical examination of the urine, often referred to as a urine dipstick. Quantification of these parameters have traditionally been used to screen for presence of a UTI.[128]

Nitrites are not normally found in the urine but may be detected when bacteria reduce urinary nitrates to nitrites.[125] A positive test for nitrite on a UA does not diagnose a UTI alone. False-positive results for nitrite may occur when the test reagent is exposed to air, phenazopyridine, or other contaminants.[125] A negative test for nitrite would not rule out a UTI if caused by a gram-positive urinary pathogen, like *Enterococcus spp*. which do not produce nitrite, or in a patient consuming a low nitrate diet.[126] Leukocyte esterase is an enzyme released by activated neutrophils and when detected in the urine may signal pyuria associated with UTI.

Microscopic evaluation of the urine can confirm the presence of white blood cells (WBCs), known as pyuria, which potentially indicates local inflammation. Pyuria may be due to non-infectious inflammatory causes, and studies have demonstrated varying rates of pyuria in asymptomatic patients (32% of young women, 90% of long-term care residents, 90% of hemodialysis patients).[106] Pyuria cutoff values vary in the literature and depend on quantification methods, but commonly include 5 or 10 leukocytes/μL among nonpregnant premenopausal women where ASB is less common.[129] In a study evaluating pyuria in non-catheterized older women (age $\geq$ 65 years) with symptomatic UTI vs. controls (asymptomatic negative culture/mixed flora or ASB), the commonly used cutoff of 10 leukocytes/μL had a sensitivity of 100% but a very low specificity of 36%, indicating this pyuria cutoff value is not clinically meaningful in this population.[130] In this study, patients with UTI had higher median urinary leukocytes compared to those with ASB (microscopy: 900 vs 26 leukocytes/μL; flowcytometry: 1575 vs 23 leukocytes/μL; $P < .001$) demonstrating that the degree of pyuria may help distinguish between UTI and ASB in older women. The investigators suggested applying a

threshold of 300 leukocytes/μL in this patient population to improve specificity (88%) to avoid overtreatment while maintaining a fair sensitivity (84%). This cutoff value of 300 leukocytes/μL is 4-fold higher than what another study has shown to produce similar sensitivity (86%) and specificity (82%) results in a younger population that did not exclude patients with antibiotic pretreatment, further highlighting the varying degree of pyuria among different patient populations.[131] Note that even at that higher cut off, the positive and negative likelihood ratios of the test (+LR 6.9, -LR 0.2) are modest. Furthermore, because laboratory equipment and electronic health records do not implement different cutoff values for different patient populations, results of abnormal urinalyses (with respect to pyuria) should be interpreted within the clinical context. Laboratory reports may implement different cutoff values tailored to specific patient populations.

Given that UTI is a clinical diagnosis, and there is notable heterogeneity in the clinical definition of UTI and pyuria quantification methods/cutoff values, it is difficult to accurately quantify the sensitivity and specificity of a UA for the diagnosis of UTI. Some studies that evaluated the diagnostic accuracy and predictive ability of UA to detect UTI did not consider the clinical definition of UTI, but rather used a positive urine culture as the reference test.[132–135] It is highly likely that many of the patients considered to have a UTI actually had asymptomatic bacteriuria. For studies that have included only patients with symptoms suggestive of UTI within their definition of infection, the clinical definition used has been heterogenous across studies and sometimes not clearly described in the methodology.[136–141]

Sensitivity and specificity ranges of UA components reported in the literature are summarized in Table 4. These wide ranges of results of sensitivity and specificity of urine dipstick and microscopic UA components reported in the literature are largely due to the varying patient populations investigated, misclassification of UTI, and differing test cutoffs and laboratory techniques. Furthermore, the differences in positive and negative predictive values associated with these sensitivity and specificity results are partially due to the varying prevalence of UTIs included in the studies. Nevertheless, studies demonstrated that pyuria is present in symptomatic patients with bacteriuria and the absence of pyuria has a high negative predictive value for UTI, meaning a negative result can be useful in ruling out a UTI in select patient populations (i.e., patients without neutropenia or complete obstructive uropathy).[132,135,137,142–145] The helpful negative predictive value of a normal UA in such patients is balanced against the high false positive rates of these tests.

Regulatory agency guidelines and clinical trials

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require the presence of pyuria as defined in their drug industry development and approval guidance documents (Table 5). In a systematic review of studies evaluating UTI definitions that are used in current research, the presence of pyuria was required for the diagnosis of UTI in only 28% of studies.[105] Of those studies, 77% applied a cutoff value of > 10 leukocytes/μL per high power field.

Urine cultures

Urine cultures are reasonable for complicated cases and/or recurrent UTIs, particularly in suspected pyelonephritis, to guide targeted therapy. In simple uncomplicated cystitis in healthy non-pregnant patients, routine cultures are not necessary. The clinical diagnosis of a UTI usually suffices.[18,127] Cultures should be reserved for cases where there is no improvement or recurrence after what can reasonably deemed appropriate treatment.

Overall Conclusion

A UA can provide information to help exclude the diagnosis of UTI in patients with functioning bone marrow. However, its diagnostic utility is limited and testing should always be performed in the right clinical context. Absence of pyuria can often rule out infection, but its presence frequently indicates non-infectious genitourinary inflammation, making it an unreliable sole indicator. The UA may be useful to help exclude a UTI, but it has limited role in establishing a UTI. Symptoms are paramount. In simple uncomplicated cystitis in healthy non-pregnant patients, routine cultures are not necessary. However, urine cultures are reasonable for complicated cases and/or recurrent UTIs and pyelonephritis to guide targeted therapy.

Table 4. Sensitivity of diagnostic tools for urinary tract infections

Test	Results	Sensitivity (%)	Specificity (%)	PPV	NPV
Dipstick	Positive leukocyte esterase	72-97	41-86	43-56	82-91
	Positive nitrite	19-48	92-100	50-83	70-88
	Positive leukocyte esterase OR nitrite	46-100	42-98	52-68	78-98
Microscopy	>5 WBCs/HPF	90-96	47-50	56-59	83-95
	10 WBC/μL	100	36	NA	NA
	50 WBC /μL	98	66	NA	NA
	100 WBC /μL	93	71	NA	NA
	200 WBC /μL	89	86	NA	NA
	300 WBC /μL	84	88	NA	NA
	400 WBC /μL	77	92	NA	NA
Imaging	Ultrasound	74.3	56.7	NA	NA
	Computerized tomography	81-84	87.5	NA	NA
	Magnetic resonance imaging	100	81.8	NA	NA

Table 5. Definitions of pyuria used by regulatory agencies.	
EMA	**FDA**
>10 leukocytes/μL	Uncomplicated UTI: "A microscopic evaluation for pyuria or dipstick analysis for leukocytes, nitrites or a catalase test should be performed" Complicated UTI: Urine dipstick positive for leukocyte esterase or >10 leukocytes/μL

Q10: What is the role of urinalysis and urine culture testing for the workup of fever?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Routine use of urinalysis and urine cultures for the workup of fever in hospitalized patients leads to unnecessary testing and antimicrobial use.[126,146,147] Studies show that UTIs, including catheter-associated UTIs (CAUTI), are infrequently the source of fever, particularly in the absence of urinary tract obstruction, recent urological procedures, or immunocompromise.[148] Consequently, urine testing should not be automatic in febrile patients, especially geriatric patients, or those with known non-urinary sources of fever and should be reserved for cases with specific urinary or related symptoms. Further research is needed to establish clear criteria for urine testing in febrile patients.

Overall Summary

UA and urine cultures are frequently obtained for hospitalized patients. Many (if not most) times, this is part of an effort to complete a "full fever work-up" or a "pan-culture" in febrile hospitalized patients. Such testing often includes UA and urine culture. For example, a prospective survey of internal medicine residents at a single institution in 2016 revealed that 96% of respondents defined a full fever work-up to include a UA irrespective of patients' symptoms.[149,150] These cultures, particularly amongst inpatients, are seldom useful in the absence of clinical suspicion of UTI.[151] Testing should occur for patients with clinical suspicion for UTI due to localizing symptoms or absence of a different source of fever.[147]

Literature is scant on the appropriateness of ordering UA and urine culture as a part of a non-specific fever workup. Studies consistently show that a significant number of catheterized or febrile patients are asymptomatic or have non-urinary sources of fever, yet urine cultures are frequently ordered.[152,153] A prospective study of 1,497 catheterized patients revealed 235 new cases of "nosocomial CAUTI", of which 90% of were asymptomatic and presumably represented colonization.[151] A study of 708 geriatric patients presenting with fever to the ED observed a high rate of urine cultures ordered despite other identifiable fever sources, with minimal impact on treatment decisions.[153] An 18-month retrospective cohort analysis showed that fever was not

associated with UTIs in ICU trauma patients during their first 14 days of stay.[154] These findings, amongst others, suggest a need to reassess the routine use of urine cultures in these patient populations.

In an intriguing 16-week study, Leis et. al stopped reporting positive urine cultures in inpatients, requiring the treating team to call for a result, if indicated. The treatment of adjudicated cases of ASB was reduced by 36% for a number needed to treat of 3, with no resulting cases on untreated symptomatic UTI or sepsis. A follow-up quasi-experimental study over six years (1,678 inpatients) at the same hospital found that the strategy prevented 99 episodes of ASB being treated and potentially 8 adverse events with 6 potentially missed cases of probable UTI.[155] No deaths occurred due to not processing inpatient urine cultures. All episodes of urinary sepsis were diagnosed when the first urine and blood cultures were ordered and these patients received adequate empiric antibiotics.

In another quasi-experimental study in which an educational campaign was rolled out hospital-wide to stop routine testing of urine to work up hospital-onset fever, the intervention resulted in a >50% reduction in urine cultures ordered, with no change in mortality rate due to UTIs.[156]

The Society of Critical Care Medicine and the Infectious Diseases Society of America recommend against routinely sending urine cultures for fever evaluation in ICU patients with catheters unless there are specific urinary symptoms. They stress the need for detailed clinical assessment to determine the need for diagnostic tests.[148]They recommend urine cultures should be ordered for the workup of fever in cases like transplant recipients, patients with neutropenia , those who have had recent genitourinary surgery, or have known obstructions, but note that urine cultures are often overused without clear indications. Similarly, the IDSA guidelines for the workup of fever in long-term care facilities recommends diagnostic laboratory evaluation of suspected UTI should be reserved for those with acute onset of UTI-associated symptoms and signs or suspected bacteremia.[157] The IDSA guidelines on febrile neutropenia recommend urine culture testing if signs or symptoms of UTI exist, a urinary catheter is in place, or the findings of UA are abnormal.[158,159] Nevertheless, there are no data to define specifically which hospitalized patients benefit from urinary evaluation during workup of fever.

Given the low probability of a UTI causing fever without any symptoms, the high rate of ASB in hospitalized or older adults, and evidence that urine testing can be safely withheld in such patients, WikiGuidelines authors suggest that UA and urine culture testing should not be routinely obtained for febrile patients without urinary symptoms, particularly those with an identifiable extra-urinary tract source for their fever. Indiscriminate urine culture testing can lead to misdiagnosis, perpetuate low value antimicrobial use, and risks both adverse drug events and the development of antimicrobial resistance.. Further studies are needed to define what criteria indicate when it is appropriate to obtain UA and urine culture in a febrile patient.

Overall Conclusion

Excessive UA and cultures for fever in hospitals causes unwarranted antimicrobial use, as UTIs are rarely the fever source. Urine tests should be limited to patients with urinary symptoms, not

routine for all febrile cases, to avoid overtreatment. Further evidence-based testing criteria development is needed.

Q11: How can diagnostic stewardship strategies be effectively implemented in the management of urinary tract infections to prevent unnecessary treatment of asymptomatic bacteriuria?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Effective management of UTI hinges on appropriate diagnostic testing and antimicrobial stewardship, aiming to prevent the misuse of antibiotics for ASB. Symptom-based testing is key to ensure appropriate urine culture testing and proper diagnosis of UTI.[106,107] A 2017 systematic review showed 45% of included patients experienced inappropriate initiation of antimicrobial treatment for ASB; various interventions such aseducation on diagnostic provided a significant absolute risk reduction of 33%.[160] Avoiding over-testing and resulting over-treatment of ASB is essential to preserving antimicrobial effectiveness.

Overall Summary

A primary challenge in the effective treatment of UTIs is diagnostic interpretation, where the presence of bacteriuria is frequently unrelated to infection. A systematic review and meta-analysis conducted in 2017 measured the appropriateness of antimicrobial administration based on IDSA guidelines for diagnosis and treatment of ASB in adults.[160] Pooled prevalence among 30 articles reviewed revealed 45% (95% CI, 39–50) of patients investigated experienced inappropriate initiation of antimicrobial therapy. Furthermore, interventions intended to address overtreatment resulted in a median absolute risk reduction of 33% (range 16-36%). Diagnostic stewardship, specifically improving prescribing practice, is vital to reduce this unnecessary treatment in the absence of true infection. An editorial published in 2019 describes a strategy of synergistically bridging diagnostic and antimicrobial stewardship strategies to improve patient outcome.[161] Diagnostic stewardship (DS) focuses on the ordering, preanalytic, analytic and post analytic process of testing whereas antimicrobial stewardship (AMS) focuses on optimizing antimicrobial use.

The incidence of ASB is increasing.[162] A primary challenge for AMS is regarding empiric therapy in a patient suffering a UTI with non-specific signs and symptoms. Strategies that aim to reduce unnecessary ordering with focused education on pre-test probability has been shown to improve outcomes.[162] Recent guidelines on DS practices have been proposed that focus on improving the total testing process (preanalytics, analytics and postanalytics) for urinary specimen diagnostics.[147]

Pre-analytical

For preanalytics, suggestions include requiring documentation of proper specimen collection and confirmation of symptoms, restricting ordering of a urine culture to patients who are

symptomatic or pregnant, or nudging prompts in the electronic medical record that advise providers to avoid ordering UA or urine cultures in asymptomatic patients. Diagnostic stewardship interventions focusing on populations at high risk for bacterial colonization, such as patients with indwelling urinary catheters, have been implemented with success and can lead to a reduction in cultures and antimicrobial use.[146]

Analytical

There are important limitations to using urine cultures to diagnose UTIs, such as long turnaround times (generally about 2-3 days from collection to susceptibility results) and interpretation of bacteria in the absence of symptomology.[147] ASB does not warrant treatment in most circumstances, and often leads to inappropriate antibiotic use. Therefore, cultures should not be routinely sent in the absence of symptoms, and such restrictions effectively reduce false positive UTI diagnoses.[156]

Post-analytical

For post-analytics, suggestions include institutional optimization of reporting, including "nudges" to aid prescribers to avoid unnecessary treatment.[161,163] In a prospective, randomized, unblinded superiority trial of the safety and efficacy of modified reporting of positive urine cultures to improve the appropriateness of treatment for ASB and UTIs in long-term care facilities (LTCFs), modified reporting of urine culture improved the appropriateness of treatment by reducing treatment of ASB.[164] The study had many limitations, including its small sample size of 100 cultures. However, other studies have shown this effect. A similar study modified the urine culture report by including the bacterial growth without providing identification, quantification, or susceptibility and compared it to the standard report, which included identification, quantitation and susceptibility.[164] The study reviewed over 500 cultures and included 100 in its analysis. The modified reporting arm had a higher appropriate treatment rate compared to the standard reporting arm: 57% versus 50% (+7.4%; RR, 1.15; P = .45). The untreated CA-ASB rate was also higher in the modified reporting arm: 45% versus 33% (+12%; RR, 1.36; P = .30). Standard reports were requested for 33% of modified reports. Additionally, there were 4 deaths and 26.9% adverse events in the modified reporting arm, compared to 3 deaths and 41.3% adverse events in the standard reporting arm.

Overall conclusion

Diagnostic and antimicrobial stewardship strategies are most likely to work effectively in tandem. Over-testing and the consequent detection of asymptomatic bacteria are both common. Diagnostic stewardship can be an effective intervention to curb over-testing and improve patient care by reducing the prevalence of asymptomatic UTI therapy.

Q12: What is the role of novel molecular tests in the diagnosis of UTI?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

The role of molecular techniques for UTI diagnosis is currently limited. Molecular diagnostics cannot distinguish true infection from ASB. Urine culture is the current reference standard for confirming the etiologic pathogen in patients with suspected infection. Although 100,000 CFU/mL has been considered the historical standard threshold for "bacteriuria" and diagnosing UTIs, lower CFU counts can still indicate significant infections in symptomatic patients.[142,165–167] In contrast, molecular techniques are generally unable to determine bacterial viability or quantitation in urine specimens.[168] These factors are crucial to differentiate colonization versus infection and to delineate pathogenic organisms versus commensal flora. The increased sensitivity of these molecular tests may lead to overtreatment by detecting clinically insignificant bacteria, especially now that metagenomics have identified endogenous genitourinary microbiota[169–173], underscoring the need for clear guidelines to avoid unnecessary therapy. More research is required to determine the ideal role of molecular testing in UTI diagnosis.

Overall Summary

Urine culture allows for both pathogen detection and quantitation. UTIs are largely caused by organisms found in the human intestinal microbiota. The quantitation of these organisms is often used to help differentiate infection from contamination by this microbiota,[174] although the accuracy of quantitation at distinguishing true infection from ASB has never been established with high quality date. The concept of using a bacterial count cutoff to define UTIs was established six decades ago by Dr. Edward Kass.[167] Traditionally, ≥100,000 CFU/mL has been considered the standard for diagnosing UTIsand continues to be the accepted threshold for defining asymptomatic bacteriuria today.[107] However, in symptomatic patients, even lower bacterial counts, ranging from 1,000 to 10,000 CFU/mL, can indicate a significant infection that warrants treatment.[142,165,166] This nuanced approach to diagnostic thresholds allows clinicians to more accurately identify and manage infections, ensuring appropriate treatment while minimizing the risks of missed diagnoses or unnecessary interventions. Further discussion on these thresholds and how they impact the definitions of UTI, microbiological response reported in clinical studies, and the assessment and management of asymptomatic bacteriuria are discussed in later sections of this manuscript (questions 18 and 25).

Nucleic acid amplification techniques (NAATs) have a wide range of functions in infectious disease diagnostics. Due to their scalability, low turnaround time, and increased sensitivity (and potentially specificity), they have quickly become adopted by varying sections of laboratory diagnostics.[175] NAATs are superior for the detection of fastidious organisms in urine that routine culture methodologies may not detect such as *Ureaplasma* spp., *Chlamydia* spp, *Mycoplasma* spp., and *N. gonorrhoeae*.

Unfortunately, NAATs are unable to distinguish viable versus non-viable organisms, which can complicate the validity of the results, particularly post therapy. Except for specific circumstances where there has been standardization, PCR or NAATs are also unable to quantitate organism burden in a specimen, which can lead to reporting confusion.[168] However, the increased sensitivity of these molecular tests may lead to the detection of clinically insignificant bacteria, increasing the risk of overtreatment. Therefore, it is essential to develop clear guidelines to mitigate this risk and ensure that treatment decisions are based on a comprehensive clinical

assessment rather than solely on molecular test results. An additional concern with NAATs for UTI diagnosis relates to antimicrobial susceptibility testing. Culture based methodology allows the phenotypic distribution of antibiotic sensitivity to be determined and for the generation of cumulative antibiograms. NAATs are limited to the detection of resistance genes which may not be expressed or relevant *in vivo* and which are limited to those which are known and present in the panel. There are no FDA or EMA approved commercial systems available for NAAT based diagnosis of UTIs. Nevertheless, several laboratories have attempted syndromic laboratory developed testing (LDT) panels for urine specimens. This has been used primarily in cases of recurrent culture-positive UTIs, to rapidly detect all pathogens present, regardless of quantitation and for genotypic resistance for therapy tailoring.[176–178]

Also of note, a recent study investigated the use of MALDI-TOF combined with mass spectrometry to determine antimicrobial susceptibility directly from urine samples.[179] Being able to use the patient's urine sample directly allowed the authors to provide phenotypic AST results to the clinician about 4.5 hours after receiving the sample, including a 2.5 hour incubation time and identification and AST conducted via MALDI-TOF MS. Combination of identification and susceptibility testing by MALDI-TOF MS had an overall categorical agreement of 94.7% when comparing to conventional AST using gradient MIC test strips. A notable challenge was that MALDI-TOF MS failed to consistently detect resistant bacteria in polymicrobial samples. Since the presence of more than one organism cannot be ruled out prior to performing the test and in fact is quite common, especially in the setting of CAUTI, the routine use of MALDI-TOF MS rapid identification and AST may be limited.

Overall Summary

The role of molecular techniques for UTI diagnosis is currently limited. Urine culture continues to have advantages in terms of their ability to determine viability of the organisms, provide quantification, and allow for both phenotypic or genotypic detection of resistance. More research is required on the targeted use of molecular techniques for the definitive diagnosis of UTIs.

Q13: What is the role of different imaging modalities such as ultrasonography and computed tomography for the diagnosis of urinary tract infections, and what is the sensitivity and specificity these imaging modalities?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

CT scans do not appear to be useful in the routine initial diagnostic workup of cystitis or pyelonephritis and may not routinely alter treatment[180,181] CT imaging may be useful if symptoms persist or worsen beyond 72 hours or if there are concerns for renal calculi, renal abscess, or an alternative focus of infection.[182–184] Contrast CT imaging is best discussed with the radiologist but may have advantages in terms of detecting renal abscesses. Ultrasound, while safer and more accessible, has limited accuracy but may be a preferrable first imaging modality in younger patients, pregnancy, and/or renal transplant recipients because there is no associated ionizing radiation, and may be able to more directly visualize the transplanted organ(s) (Table 4).

Magnetic resonance with or without contrast and/or diffusion-weighted imaging is less effective for early disease detection and stone visualization but may also have an advantage in identifying graft infection (Table 4).[185,186] Authors caution clinicians to only obtain radiographic studies if they are likely to alter management for a patient with known or suspected UTI.

Overall Summary

The utility of imaging in evaluating UTIs may vary depending on the patient, any associated risk for complication or pregnancy, and the specific imaging modality. Modalities which can be employed include computed tomography (CT) scan with and without IV contrast, ultrasound, and magnetic resonance imaging (MRI) with or without contrast.

Computed tomography (CT)

For initial diagnosis of acute pyelonephritis, CT of the abdomen and pelvis is generally not beneficial, as it can often be negative and does not change management even if positive.[180,181,184,187] The sensitivity of CT imaging for the diagnosis of acute pyelonephritis has been reported to range from 81 to 90%.[188–190] More importantly, there is a high rate of clinical response to acute pyelonephritis treated with effective therapy, so radiographic results do not alter management.

In contrast, for patients not responding to initial therapy, CT of the abdomen and pelvis with or without contrast enhancement may help elucidate renal abscess, stones, congenital abnormalities, emphysematous disease, and/or other anatomic or pathologic features.[181–184,187,191–195] It may also provide an alternative diagnosis. If CT imaging was not obtained during the initial work-up, lack of clinical improvement to initial empiric therapy after a suitable time period (e.g., 72 hours) or clinical deterioration are reasonable indications to pursue CT imaging to evaluate complications, such as abscess formation, urinary stones, or other causes of urinary obstruction.[180–184,187,191,193–196]

Ultrasound

Ultrasound of the abdomen and pelvis is generally not helpful in the initial evaluation of pyelonephritis because it is commonly negative, has been shown to be less accurate than CT imaging for the diagnosis of acute pyelonephritis, renal abscesses, and emphysematous disease, and is unlikely to change initial management.[180,182,187,190,197,198] Despite these limitations, ultrasound studies avoids radiation to the abdomen and pelvis which may be relevant in younger or pregnant patients. In the case of a pregnant patient, while the lack of ionizing radiation may be appealing, the utility may be limited by physiologic hydronephrosis in pregnancy.[199] Nonetheless, as a first step, it can still have benefit. Other advantages of Ultrasound include that it can be performed at the bedside and does not require any IV contrast. Venkatesh et al. observed suggestive ultrasound (US) features in 66% of cases, and Majd et al. noted a sensitivity and specificity of 74.3% and 56.7%, respectively, for US diagnosis. In a study by Majuntah et al, the sensitivity of ultrasound in diagnosing acute pyelonephritis was 64.51%.[188,200,201]

Magnetic Resonance Imaging (MRI)

MRI findings with or without contrast enhancement appear to be similar to that of CT and include the ability to detect renal edema, hemorrhage, enlargement, abscesses, and perinephric fluid collections and may be especially useful if the patient should not receive iodinated contrast or ionizing radiation (e.g., if pregnant or known hypersensitivity to iodinated contrast). Gadolinium enhancement may be particularly useful to assess renal tubular obstruction and other areas of renal parenchymal involvement.[187,202] Diffusion-weighted imaging (DWI) via MRI can detect acute pyelonephritis, renal abscess, and pyonephrosis through expected signal intensity patterns for simple fluid (low-intensity on T1-weighted images, high-intensity on T2-weighted images); however it appears to have lower accuracy for detection of renal stones and emphysematous changes such as gas production due to their reported variable detection via MR and/or susceptibility to magnetic artifact. [185,186,203] Murakami et al report on the sensitivity of MR imaging for GU abnormalities. MRI achieved sensitivity 65.2% and specificity 73.9% as a screening test for VU while DW-MRI achieved sensitivity 100% and specificity 81.8% in the diagnosis of upper UTI.

As for any test, radiographic studies of any kind should only be obtained if they are likely to alter management for a patient with known or suspected UTI.

Q14: What are the limitations of usual diagnostics in patients with indwelling urinary catheters or ileal conduits?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Urinalysis has a very low specificity in diagnosing UTIs in patients with indwelling urinary catheters or ileal conduits, but has excellent negative predictive value.[204] This suggests that a negative UA can rule out catheter associated urinary tract infections (CAUTI) for patients with functioning bone marrow, but given the low specificity of UA in patients with urinary catheters or ileal conduits, a positive UA does not mean the patient has a CAUTI. In addition, urine cultures are not reliable tests for patients with chronic urinary catheters or ileal conduits.[205–207] In these cases, bacteriuria is almost always present regardless of symptoms and are a likely source of inappropriate initiation of antimicrobial treatment

Overall Summary

Urinary catheters

Pyuria is a common finding in catheterized patients regardless of symptoms. In a prospective study analyzing 761 newly catheterized patients, pyuria, defined as WBC count greater than 10 per microliter per high-power field, had a sensitivity of about 37% for diagnosing a CAUTI.[204] In another study examining UA in patients hospitalized in surgical ICU, presence of nitrite had sensitivity of 29.5% and the presence of leukocyte esterase, WBC count, or any other parameter did not correlate with CAUTI.[208] However, in another study that examined UA in trauma

patients in intensive care unit (ICU), a negative UA reliably excluded CAUTIs with 100% negative predictive value.[209] Similarly, bacteriuria is common in patients with urinary catheters as well. In a prospective study that followed newly catheterized patient with daily urine samples obtained for culture, incidence of bacteriuria was noted to be 5% per day of catheterization and more than 90% of those with bacteriuria did not report any symptoms consistent with UTI.[205] Biofilms present in catheters provide a survival advantage and may contribute to ASB.[210] Changing the catheter before urine collection can improve diagnostic accuracy and antibiotic response. In another study that performed sequential quantitative cultures and UA from patients with long-term urinary catheters, pyuria and bacteriuria was found to be common regardless of symptoms. During symptomatic UTIs, neither UA nor urine cultures exhibited changes specific to infection.[211]

It has been claimed that CAUTI may have minimal symptoms.[152] However, there is potentially circular logic in this and related studies. If a CAUTI is defined by the number of WBCs in urine along with a positive culture, symptoms are not required to diagnose the infection. If, on the other hand, a patient is considered to have ASB in the absence of symptoms, and therefore, by definition, not to have a CAUTI, such studies are non-informative and distracting. Most WikiGuidelines authors believe CAUTI's should not be diagnosed in the absence of symptoms, if the patient is conscious and is capable of experiencing symptoms.

Ileal conduits

In a retrospective study that followed patients who underwent urinary diversion, leukocyte esterase was positive in approximately 90% of patients after ileal conduit and orthotopic ileal neobladder at two weeks of surgery.[212] After 12 months of surgery, every patient was noted to be positive. Similarly, urine cultures were positive in 52.5% with ileal conduit and 60.5% with orthotopic ileal neobladder two weeks after surgery, but after 12 months, all urine cultures were positive and noted to be polymicrobial. Therefore, cultures should be obtained only when signs of clinical infection are present and these cultures may be polymicrobial, requiring clinical judgement and interpretation.

Overall conclusion

The data on diagnosing CAUTI via specific components of the UA are severely confounded in many ways, including the lack of standardization regarding the diagnosis of infection, and the potentially circular definitions of the infection. Measuring the accuracy of a test to diagnose an infection when components of that test are used in the definition of the infection is conceptually problematic. Nevertheless, a completely normal UAs may be useful to help exclude a CAUTI. However, due to poor specificity, positive tests don't confirm UTI because of inflammation due to the presence of the catheter and the near 100% prevalence of ASB.

eAppendix 3: EMPIRIC TREATMENT

A proposed framework for selecting empiric treatment regimens is presented in eFigure 1in the supplemental materials.

Q15: What are reasonable empiric treatment regimen(s) for pediatric or adult patients diagnosed with a urinary tract infection?

Clear Recommendation

Executive Summary

Empiric treatment regimens for pediatric and adult patients should contain antimicrobials that have historically demonstrated efficacy and safety in the treatment of UTIs , achieve adequate urinary concentrations, and provide reliable activity against the most common pathogens based on local resistance rates (eFigure 1, eFigure 2). Additionally, empiric therapy should consider antimicrobial stewardship principles to select the narrowest spectrum agent with adequate spectrum of activity. Presence of risk factors for antimicrobial resistance along with clinical severity also play an important role in the selection of empiric choices.[104,213] For patients with uncomplicated cystitis, nitrofurantoin is a reasonable drug of choice, based on robust evidence of efficacy and its ability to spare use of more systemically active agents for treating other infections.[214] For patients with pyelonephritis, trimethoprim/sulfamethoxazole or a first-generation cephalosporin represent reasonable first-line agents but should be dependent upon local resistance rates. Due to low resistance rates and clinical effectiveness, ceftriaxone is the recommended empiric choice for patients who require intravenous therapy, barring any risk factors for multi-drug resistance.[215,216] In general, agents with antipseudomonal activity should only be used in patients with risk factors for nosocomial pathogens. However, it may be reasonable to use carbapenem therapy empirically in hemodynamically unstable patients for whom there is a specific concern regarding extended-spectrum beta lactamase (ESBL)-producing bacteria. Overall, selection should be guided by local susceptibilities and patient-specific risk factors.

Overall Summary

Selection of empiric therapy for the treatment of cystitis and pyelonephritis in pediatric patients should be influenced by local antibiogram data, with selection of the narrowest-spectrum agent targeting the primary pathogen of concern [217]. UTIs in both adult and pediatric patients are primarily caused by enteric Gram-negative bacteria, with *E. coli* being the most common pathogen.[217] Other causative organisms include *Klebsiella pneumoniae*, *Klebsiella oxytoca, Proteus mirabilis*, and, less frequently, Gram-positive bacteria such as *Enterococcus faecalis*. The importance of empiric antibiotic therapy in managing UTIs cannot be overstated, as it reduces symptoms and prevents complications while awaiting culture results.[104] In pediatric patients, timely initiation of empiric therapy is crucial to prevent renal scarring and other long-term complications, particularly in children with pyelonephritis and children <2 years of age.[218]

Resistance patterns of UTI pathogens have evolved, presenting significant challenges. In adults, resistance to commonly used antibiotics such as trimethoprim/sulfamethoxazole (TMP/SMX) and ampicillin is increasingly reported.[216] Therefore, in patients with prior history of UTI, use of historic microbiological and susceptibility data for that patient to influence selection of empiric therapy is advised. ESBL-producing organisms further complicate treatment, necessitating the

consideration of broader-spectrum antibiotics in empirical therapy.[219] Pediatric UTI pathogens show similar resistance trends, with increasing resistance to TMP/SMX, ampicillin, and cephalosporins.[220] The emergence of ESBL-producing organisms and resistance to nitrofurantoin and cephalosporins highlights the need for careful selection of empiric antibiotics in patients at risk.

For adults with cystitis, empiric treatment choices should be guided by local susceptibility patterns and whether the patient has risk factors for multi-drug resistant bacteria. Predictors include a history of recurrent UTIs, past-year hospitalization, along with prior antibiotic use.[221] These predictors were found in young females in a retrospective cross-sectional study of Enterobacterales -associated outpatient UTIs from 2014-16 involving 1207 cases.[221] Similarly, a retrospective case-control study conducted in South Carolina from April 2015 to February 2016 analyzed 351 adult patients with community-onset UTIs caused by Enterobacterales.[222] Of these, 71 (20.2%) had TMP/SMX-resistant urinary isolates, with prior urinary infection/colonization with TMP/SMX-resistant Enterobacterales (OR=8.58) and TMP/SMX use within the past 12 months (OR=2.58) identified as significant predictors of resistance.[222]

The preferred antibiotic for empiric treatment of cystitis in adults is nitrofurantoin. The optimal empiric antibiotic will vary by region based on local resistance patterns and patient predictors of antimicrobial resistance. This selection should also be further individualized based on patient factors such as allergies, tolerability, availability, and cost. For patients without risk factors, nitrofurantoin is a reasonable first-line agent, with extensive efficacy data and the ability to spare more systemically active agents to treat other infections. A systematic review of 27 controlled clinical trials conducted between 1946 and 2014, involving 4807 patients, assessed the short-term (≤14 days) use of nitrofurantoin for lower UTIs. The review found that nitrofurantoin demonstrates good clinical and microbiological efficacy against common uropathogens, with clinical cure rates between 79% and 92%, and is generally equivalent to trimethoprim/sulfamethoxazole, ciprofloxacin, and amoxicillin when administered for 5 to 7 days. Nitrofurantoin also has low toxicity, which is primarily mild and gastrointestinal, with rare occurrences of resistance and no observed hypersensitivity reactions such as pulmonary fibrosis or hepatotoxicity. However, it should be avoided with severe renal impairment (estimated glomerular filtration of <30) or if any suspicion of pyelonephritis is present.

TMP/SMX remains an alternative first-line option, and should be considered in adult patients without risk factors for resistance and where local susceptibility data permits. A prospective randomized trial conducted at a student health center compared 3-day oral regimens of trimethoprim/sulfamethoxazole, nitrofurantoin, cefadroxil, and amoxicillin for treating acute cystitis in women.[223] Six weeks after treatment, cure rates were highest with trimethoprim/sulfamethoxazole (82%) compared to nitrofurantoin (61%), cefadroxil (66%), and amoxicillin (67%), with persistence of significant bacteriuria being least common in the trimethoprim/sulfamethoxazole (3%) and cefadroxil (0%) groups. Risk factors for TMP/SMX resistance should also be considered, including prior urinary infection or colonization with TMP/SMX-resistant Enterobacteriaceae (OR=8.58) and TMP/SMX use within the past 12 months (OR=2.58).[222]

Oral beta-lactams historically have not been recommended first-line due to reports of inferior clinical and microbiological cure rates, although the clinical significance of persistent bacterial colonization in the genitourinary tract is unclear. A randomized, double-blind trial involving 300 women with acute uncomplicated cystitis compared 3-day regimens of ciprofloxacin and cefpodoxime, finding a 30-day clinical cure rate of 93% for ciprofloxacin and 82% for cefpodoxime, with a difference of 11% (95% CI, 3%-18%).[224] The microbiological cure rate was higher for ciprofloxacin at 96% compared to 81% for cefpodoxime (difference of 15%; 95% CI, 8%-23%). Ceftriaxone should not be used to determine susceptibility for oral second or third-generation cephalosporins given the propensity to overcall cefdinir, cefixime, and cefpodoxime susceptibility and stark differences in the drugs' pharmacokinetics.[225–227] Similarly, a randomized, single-blind trial comparing a 3-day regimen of amoxicillin-clavulanate to ciprofloxacin for treating acute cystitis in 370 women found that clinical cure was achieved in 58% of the amoxicillin-clavulanate group versus 77% of the ciprofloxacin group (P<.001).[228] Even among those with strains susceptible to amoxicillin-clavulanate, cure rates were lower (60% vs 77%; P=.004). These factors, along with increased resistance to beta-lactams, make nitrofurantoin or TMP/SMX first line. Despite the conflicting evidence with oral beta-lactams in the treatment of adults with UTI, it may be reasonable to consider the use of oral beta-lactams as an alternative when local resistance rates or patient-specific factors preclude the use of nitrofurantoin or TMP/SMX. Given their association with increased selection for multi-drug resistance, propensity for toxicity, and widespread resistance, fluoroquinolones are generally reserved for patients for which no other alternative options exist.

For adult patients with risk factors for antimicrobial resistance, fosfomycin is an adequate initial agent for cystitis. However careful review of prior cultures should help guide therapy and a new culture should be obtained. A case-control study conducted in 11 Spanish hospitals from February 2002 to May 2003 investigated risk factors for community-acquired infections caused by ESBL-producing *E. coli*.[229] The study included 122 cases and identified risk factors such as age over 60 years, female sex, diabetes mellitus, recurrent UTIs, previous urinary tract procedures, outpatient follow-up, and prior use of aminopenicillins, cephalosporins, and fluoroquinolones. A 93% cure rate was observed for cystitis treated with fosfomycin and amoxicillin-clavulanate for susceptible isolates. However, a multinational, open-label, analyst-blinded, randomized clinical trial compared the efficacy of nitrofurantoin and fosfomycin in treating uncomplicated cystitis in 513 nonpregnant women and found lower cure rates.[214] Participants were randomized to receive either nitrofurantoin (100 mg three times daily for 5 days) or a single 3-g dose of fosfomycin, with clinical evaluation and urine culture collected 14 and 28 days post-therapy. Clinical resolution at 28 days was achieved in 70% of nitrofurantoin patients versus 58% of fosfomycin patients (difference, 12% [95% CI, 4%-21%]; P = .004), while microbiologic resolution was 74% versus 63%, respectively (difference, 11% [95% CI, 1%-20%]; P = .04). Therefore, though fosfomycin is an adequate empiric choice, careful review of prior cultures should help direct empiric choices and treatments should be tailored once cultures are reported.

A single dose of an intramuscular or intravenous aminoglycoside may also be considered as an alternative treatment for cystitis in patients with multi-drug resistance.[230,231] While some studies found lower rates of treatment response, this is often the case with "traditional" regimens as well and multiple publications have suggested there are compelling reasons to use the single

dose strategy in patients with anatomic abnormalities.[232,233] A systematic review investigated the efficacy of a single aminoglycoside dose for UTI treatment and found thirteen studies involving 13,804 patients, aged from 2 weeks to over 70 years, and a pooled microbiologic cure rate of 94.5% ± 4.3% with a 30-day sustained cure rate of 73.4% ± 9.6%.[230] Lower cure rates were seen in patients with urinary tract abnormalities ($P < 0.01$). Toxicity was minimal, with 0.5% of cases reporting nephrotoxicity, vestibular toxicity, or injection site reactions, and no hearing loss observed.

For pediatric patients with cystitis, nitrofurantoin, cefadroxil, cephalexin, or TMP/SMX are considered first-line empiric agents. In children, nitrofurantoin may carry additional complications such as dosing frequency, palatability, and cost considerations that may make other options more feasible. Similarly, in children with proven or suspected pyelonephritis, a first-generation cephalosporin (i.e., cefadroxil, cephalexin) or trimethoprim/sulfamethoxazole are considered preferred first-line options.[218] Oral amoxicillin and amoxicillin/clavulanate may be considered as a first-line alternative for cystitis in areas where resistance rates to *E. coli* remain low. If parenteral therapy is required for a child admitted and unable to tolerate oral therapy, intravenous (IV) ceftriaxone or IV cefazolin, depending upon local resistance rates, represent appropriate first-line options.[218]

In patients with cystitis, when *E. coli, K. pneumoniae, K. oxytoca,* or *P. mirabilis* are isolated from a urine culture and the cefazolin MIC is less than 16 mcg/mL, susceptibility is presumed for oral first, second, and third generation oral cephalosporins.[234] Ceftriaxone should not be used to determine susceptibility for oral second or third-generation cephalosporins given the propensity to overcall cefdinir, cefixime, and cefpodoxime susceptibility and stark differences in the drugs' pharmacokinetics.[225–227] Oral first generation cephalosporins have favorable pharmacokinetics and achieve high (>90%) concentrations of active drug in the urine.[235] Thus, although Enterobacterales species have demonstrated increasing rates of resistance to cefazolin, the high urinary concentrations achieved by first generation cephalosporins allow for maintained efficacy for cystitis. Oral second and third generation cephalosporins have diminished urinary excretion secondary to increased protein binding and poor oral bioavailability. The percentage of active drug recovered in the urine following a dose is only 42-57% for cefuroxime, 3-18% for cefdinir, 29-33% for cefpodoxime, and 27% for cefixime.[236,237] Additionally, available susceptibility data demonstrates lack of benefit, as it relates to *E. coli* susceptibility, between oral first generation and oral advanced generation cephalosporins. Thus, when taken together, there is no appreciable benefit to justify the use of an oral advanced generation cephalosporin, over an oral first-generation cephalosporin, for the treatment urinary tract infections in pediatric patients.

For adults with pyelonephritis or cystitis complicated with either bacteremia or systemic symptoms, empiric antimicrobial selection should be guided by severity of illness in addition to risk factors for drug resistance. Outpatient management is feasible in patients without clear reasons for admission (e.g., without severe pain, inability to take oral medications, or hemodynamically instability).[238] In these cases, fluoroquinolones or TMP/SMX are recommended if local susceptibilities permit and the patient lacks predictors for drug resistance.

A randomized, double-blind trial conducted compared the efficacy and safety of a 7-day ciprofloxacin regimen with a 14-day trimethoprim/sulfamethoxazole regimen in treating acute

pyelonephritis in women. Among 255 analyzed premenopausal women, bacteriologic cure rates were significantly higher with ciprofloxacin (99%) compared to trimethoprim/sulfamethoxazole (89%) (95% CI, 0.04-0.16; P = .004).[239]

In patients who are unable to tolerate oral therapy or who are hemodynamically unstable at the time of evaluation, parenteral antimicrobials are required. In many locations, ceftriaxone is a reasonable first-line parenteral option for the treatment of community onset UTI. A retrospective study analyzed antimicrobial resistance in *Escherichia coli* urine isolates in the United States from 2011 to 2019. Among 1,513,882 isolates, nonsusceptibility rates to ceftriaxone were less than 6.4%.[216] In a prospective, multicenter, double-blind, randomized study compared the efficacy and safety of ertapenem and ceftriaxone in 271 adults with acute pyelonephritis and complicated urinary tract infections found 87.9% of ertapenem patients and 88.7% of ceftriaxone patients had a favorable microbiological response.[215] Therefore, for most patients admitted with complicated urinary tract infections or pyelonephritis, ceftriaxone serves as a suitable initial antimicrobial therapy due to high susceptibility and cure rates.

Agents with antipseudomonal activity are not routinely needed for patients with community onset infection, absent specific risk factors (e.g., chronic indwelling catheter, prior colonization or infection by a nosocomial pathogen, multiple prior courses of antibiotic therapy). However, it is reasonable to initiate empiric carbapenem therapy for patients who are hemodynamically unstable and for whom ESBL infection is a concern (e.g., multiple prior antibiotic courses, prior colonization or infection with an EBSL pathogen).[215,240–242] An alternative reasonable strategy may be to administer a single dose of aminoglycoside plus ceftriaxone to provide coverage for a possible ESBL and “buy time” for a urine culture to determine the etiologic agent to tailor therapy.

Resistance to carbapenems may require novel antibacterials. Options for patients with suspected carbapenem resistance include ceftazidime/avibactam, meropenem/vaborbactam, aminoglycosides, imipenem/cilastatin/relebactam, and cefiderocol.[219]
In children with proven or suspected pyelonephritis, empiric choices should be guided by local antibiogram data, with selection of the narrowest-spectrum agent that maintains adequate activity against organisms of concern. If parenteral therapy is required for a child admitted and unable to tolerate oral therapy, intravenous (IV) ceftriaxone or IV cefazolin, depending upon local resistance rates, represent appropriate first-line options.[218] No minimum duration of IV therapy is necessary for children with cystitis or pyelonephritis, and IV and oral therapy are considered equally efficacious.[273] If a child is started on parenteral therapy empirically, every attempt should be made to convert to oral as soon as able. Otherwise, children with acute pyelonephritis can be treated effectively with oral therapy. Oral empiric options include first-generation cephalosporins (i.e., cefadroxil, cephalexin) or trimethoprim/sulfamethoxazole.[218] Oral amoxicillin and amoxicillin/clavulanate may be considered as a first-line alternative for pyelonephritis in areas where resistance rates to *E. coli* remain low.

Overall conclusion

Empiric treatment of UTIs should be guided by local resistance patterns and patient-specific factors such as severity and risk of multi-drug resistance. Prompt initiation of appropriate

empiric therapy is essential to ensure effective management and prevent complications in both adult and pediatric populations.

Q16: What are reasonable empiric treatment regimens for treatment of a catheter-associated urinary tract infection (CAUTI)?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

There is an absence of high-quality data to inform empiric treatment in patients with CAUTI. Observational data suggests it may be preferable, where possible, to replace or discontinue existing catheters prior to the collection of cultures and initiation of antimicrobial treatment.[243] UTIs diagnosed after catheter exchange are likely to respond similarly to non-catheterized patients. Empiric treatment decisions can be made based on review of the individual patient's urinary tract anatomy or dysfunction, allergies, medication list for interactions, microbiological and prior treatment history, the type of urinary tract infection (e.g., cystitis vs. pyelonephritis), and the clinical severity of presentation.

Overall Summary

Catheter removal/exchange

A small, randomized trial conducted in 54 nursing home residents with chronic indwelling catheters (mean days since last replacement about 30 days in both groups) demonstrated improved clinical and bacteriological outcomes in the group that underwent catheter replacement prior to initiation of antimicrobial treatment as compared to the group that did not undergo catheter replacement.[243] Among the observed benefits, the group who underwent catheter replacement prior to initiation of antimicrobial treatment had lower rates of polymicrobial bacteriuria as early as day 3, improved clinical status 72 hours after initiation of treatment, shorter time to being afebrile, and a lower rate of symptomatic clinical relapse at 28 days. Both groups received intravenous fluoroquinolone treatment until afebrile for 24 hours. Patients were then transitioned to an oral fluoroquinolone (or active alternative if the organism was found to be resistant) for a total of 14 days. While the aforementioned trial is the only prospective, randomized trial to investigate the effect of catheter replacement on relevant clinical outcomes, the epidemiologic association between catheter *in situ* duration and polymicrobial bacteriuria with subsequent urinary tract infections has been documented.[106,205] It is reasonable to rationalize that removal or reduction in the bacterial inoculum and presence of biofilms may contribute to improved clinical outcomes with very little downside. While existing guidelines from IDSA suggest catheter replacement only if the catheter has been in place for longer than 2 weeks[213], the available evidence likely does not support a specific timeframe for which catheter replacement can be recommended. Decisions about replacement should be likely contextualized to any patient risks from reinsertion (e.g., known complicated anatomy). As with any device, the time of removal could serve as a helpful decision point for evaluating for ongoing necessity.

Antibiotic management

Empiric decisions can be made based on review of the individual patient's: urinary tract anatomy or dysfunction; allergies; medication list for interactions; microbiological and treatment history; the type of urinary tract infection (e.g., cystitis vs. pyelonephritis); and the clinical status. Catheterization is an independent risk factor for treatment failure but it's unclear if this is dependent on or can be overcome by catheter exchange and/or careful empiric antibiotic selection. CAUTI's can be caused by the same pathogens associated with non-CAUTIs, such as E coli, but may also include other pathogens such as *S aureus*, *Klebsiella* spp and coagulase negative Staphylococci.[244,245]] It's reasonable to consider similar empiric therapy regimens and treatment principles, but consideration must be given to prior cultures and the possibility of Gram positive organisms . No high-quality data exists to guide the preferential use of oral or intravenous therapy empirically. However, the myth that intravenous therapy is superior to oral therapy has been debunked in several, more complex infection types, such as osteomyelitis, bacteremia, and endocarditis.[[246]]

One large retrospective study evaluated commonly used oral agents among older adult patients without upper tract involvement or recent antibiotic use. They found a 9% reduced risk of treatment failure when fluoroquinolones were used compared to TMP/SMX. The potential modest reduction in risk should be weighed against the notable harms, such as tendonitis and cardiac arrythmias, associated with fluoroquinolone use and location-specific resistance rates. Given the multiple advantages of oral therapy for patients and health systems, the authors prefer oral empiric therapy for hospitalized and non-hospitalized patients with CAUTI who are clinically stable, able to ingest and absorb oral medications,[[247]] and where potentially relevant drug-drug interactions have been considered.

No validated criteria exist to reliably select patients with CAUTI at high risk of drug resistant infections. For community onset infections, the clinicians may choose to review past urine cultures and risk factors for multidrug resistant organisms. For nursing home or hospital-associated infections, local institutional antibiograms, ideally urinary antibiograms, can help guide empiric therapy decisions. A study involving 317 nursing home clinicians evaluated the impact of urinary antibiograms on empirical antibiotic choices for UTIs.[248] The study found that clinicians provided with either a traditional antibiogram or a weighted-incidence syndromic combination antibiogram (WISCA) were significantly more likely to select both active and optimal antibiotics compared to those without any tool. Traditional antibiogram (OR, 1.94; 95% CI, 1.42-2.66; P < .001) or a weighted-incidence syndromic combination antibiogram (OR, 1.7; 95% CI, 1.24-2.33; P = .003) were statistically superior to no tool when selecting an optimal empirical antibiotic. Thus, urinary antibiograms enhance empirical antibiotic selection without increasing the use of broad spectrum antimicrobials in nursing facilities.

Q17: What are the established risk factors for urinary tract infection due to multi-drug resistant organisms and when should empiric treatment account for these pathogens?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Although no validated models exist, prior healthcare exposure, previous antibiotic use, and a history of urinary tract infection or known colonization seem to be the most consistent and important predictors of development of a UTI due to a multi-drug resistant organism (MDRO).[249–251] Due to heterogeneity in the populations and methods of available studies, the timing and/or combination of the exposure(s) and the subsequent effects on the outcome are unclear. There is insufficient data available to clearly guide decisions on when empiric treatment should include the possibility of an MDRO. In the absence of such data, it may be reasonable to suggest that the severity of an infection may be an important driver of empiric antibiotic choice when combined with local resistance patterns, proposed epidemiologic risk factors, and an individualized microbiologic history.

Overall Summary

Ideally, well-validated prediction models should guide empiric antibiotic choices when antibiotic-resistance is suspected in urinary tract infections (UTIs) as for in other types of infections, in order to avoid unnecessary use of broad-spectrum antibiotics when the risk of multidrug-resistant organisms is deemed low or to increase appropriateness of therapy when the risk is deemed high pending microbiological results. Unfortunately, no score is perfect and it is cumbersome to develop a model that generalizes across multiple populations, since predicted risks are unlikely to calibrate satisfactorily with observed risks in every population and setting.[252]

Risk factors for multidrug resistant organisms (MDROs)

Several models have been developed so far to predict to predict non-susceptibility to first-line agents against causative pathogens of UTIs such as trimethoprim/sulfamethoxazole, fluoroquinolones, nitrofurantoin, and third-generation cephalosporins especially in the context of outpatients or patients visiting the emergency department.[253–255] Moreover, the availability of big data through electronic health records has enabled the development of clinical decision support tools based on machine learning-driven approaches to predict antibiotic resistance in UTIs.[255,256]

When considering systematic reviews and meta-analyses on this topic, we sought to discuss those which included multiple countries or geographical areas and assessed for risk factors for MDROs in UTI. We identified 3 systematic reviews or similar papers which met these criteria.

The first systematic review addressing risk factors for UTIs by MDROs was published in 2018, analyzing literature from 1966 to 2016 and including 25 articles.[249] Nevertheless, only 3 of them used the definitions set by the international consensus[257] describing multi-drug resistant (MDR), extensively drug resistant (XDR) and pandrug resistant (PDR) bacteria. The authors decided to stratify risk factors as probable, possible, and unlikely according to pre-defined criteria (e.g., the number of studies identifying a given predictor). Overall, the following were considered as probable risk factors: the presence of a urinary catheter, hospitalization in the previous 12 months, prior use of antibiotics, and residency in a nursing home. The following were considered as possible risk factors: a history of UTI in the previous 12 months, male gender, and age. Limiting the analysis to more recent studies adopting the definitions proposed

by Magiorakos et al.[257], the ensuing risk factors for MDR UTIs were: urinary catheterization, hospitalization or UTI in the previous 12 months, prior antibiotic exposure, nursing home residency, older age, and diabetes mellitus. The major limitation of this systematic review was the clear lack of standardization, both of antibiotic resistance and of risk factors, for instance the different exposure windows to capture prior antibiotic usage.[249]

In 2020, another systematic review specifically investigated risk factors of extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* among community-acquired UTIs[250], starting from the premise that *Escherichia coli* is by far the most common cause of UTI in this setting[217], and acknowledging that World Health Organization priority list of antibiotic-resistant pathogens classifies third-generation cephalosporin-resistant Enterobacterales as a critical priority.[258] The authors included 16 observational studies (14/16 published after 2012) for a total of 12,138 patients from several countries[250]. The main risk factors for a community acquiried UTI involving ESBL-producing *E. coli* were: prior use of antibiotics (ORs ranging from 2.2 [95% CI: 1.1 to 4.5] to 21.4 [95% CI: 5.4 to 85.2]); prior hospitalization (ORs ranging from 1.7 [95% CI: 1.3 to 2.3] to 3.9 [95% CI: 1.2 to 12.7]); and UTI history (ORs ranging from 1.3 [95% CI: 1 to 1.6] to 3.8 [95% CI: 1.8 to 8.1]). Unfortunately, the classes of antibiotics and the exposure windows were poorly defined across included studies.

Finally, specific to pediatrics, an evidence synthesis including 23 articles from 1985 to 2015 found that ESBL producing Enterobacterales cause approximately 15% of pediatric UTIs with the following risk factors: vesicoureteral reflux (OR 2.79 95%CI), history of UTI (OR 2.89 95%CI), and recent antibiotic use (OR 3.9 95%CI).[259]

General considerations

Validated models accurately predicting MDROs involvement in UTIs in individual patients are lacking and the evidence syntheses describing risk factors reflect the low quality of underlying primary studies, limited by high heterogeneity and inconsistent definitions.

The limited evidence does suggest that prior healthcare exposure, including previous antibiotics use, and prior UTIs (especially by the same pathogen) seem to be important predictors of MDROs, although the exact timing of exposure is not well defined. Local epidemiology also matters, and that particularly applies in nosocomial settings, wherein UTIs are often catheter-related and risk factors for MDROs are commonly present. For example, the probability of an MDRO in a patient in a country like Denmark will differ substantially from the probability of an MRDO UTI in a patient on the Indian subcontinent but there may also be important differences between centers within the same geographic area related to population makeup (including travel patterns to more endemic areas), referral patterns, and patient comorbidities.[251] A study involving 528 international travelers aimed to create a clinical prediction rule for identifying those at risk of ESBL-producing Enterobacterales colonization upon return to the United States. Using data from pre- and post-travel questionnaires and destination-specific information, regression and logistic regression modeling identified a 10-feature prediction rule.[251] This prediction rule had an internally cross-validated area under the receiver operating characteristic curve (cvAUC) of 0.70 (95% confidence interval 0.69-0.71). A simplified four-feature model performed similarly to the 10-feature model, with a cvAUC of 0.68 (95% confidence interval

0.67-0.69). This highlights the importance of travel exposures and their associated risk of colonization with antimicrobial resistance.

Extrapolating from studies on infections in general or on bloodstream infections, in the absence of active nosocomial transmission, the more recent a colonization has been documented, the more potentially relevant. For instance, a study looking at 370 consecutive patients with known Enterococcal bacteremia found that known VRE colonization within 30 days was associated with a positive likelihood ratio for VRE as the cause of 4.2 (95%CI 2.9-6.0) and negative likelihood ratio of 0.32 (95%CI 0.16-0.50).[260] Incorporating more remote VRE testing reduced the positive likelihood ratio to 3.3 (95%CI 2.5-4.3) without really improving the negative likelihood ratio. In a two city study of 1832 patients with Gram-negative bloodstream infections, a prior positive culture within 12 months that was resistant to a drug of interest had a 66% positive predictive value (95%CI 61-70%) and 86% negative predictive value (95%CI 85-88%) for predicting resistance to that drug in the current infection.[261,262] The negative predictive value slightly increased as the period of time between the prior culture and the current event increased from 80-85% within 2 weeks to almost 90% at 12 months. However, the positive predictive value decreased from ~80% within 2 weeks to 65% weeks 2-4 and down to approximately 30-40% by 12 months.

Overall conclusions

Overall, there is a lack of externally validated and universally accepted parsimonious models aimed at aiding physicians in the appropriate coverage of MDROs when faced with a patient with a UTI. To make things more challenging, the epidemiological context has a huge impact on the baseline risk of MDROs (even for community-onset UTIs) and with equal values of a given prediction score, the threshold to commence an empiric therapy with broad-spectrum agents may vary according to the severity of clinical presentation, being lower in patients with septic shock in which a delayed appropriate antimicrobial treatment is a stronger independent predictor for unfavorable outcomes than the resistance determinant itself.[[263,264]] Indeed, many clinicians seem to intrinsically understand this concept. In simulated scenarios, clinicians were more comfortable "being wrong" when patients were less acutely ill (e.g., cystitis or hemodynamically stable pyelonephritis vs. septic shock).[262,265]

Consequently, acknowledging the limitations of the evidence, we hypothesize that patients without severe infection may be treated with first-line agents unless they have a compelling reason to suspect MDRO. By contrast, since delay in appropriate treatment may negatively impact prognosis in more severe patients (in particular those with septic shock), empiric coverage could account for the most common MDROs within that patient population at the site of treatment while accounting for any individual patient factors. The threshold with which one uses broader-spectrum empiric coverage therefore likely needs to be individual tailored to the probability of MDRO infection, the risks of the drugs being used (e.g., aminoglycoside toxicity), and the severity of the illness (consequences of initially being wrong). Antimicrobials could then be streamlined when microbiological results are available.

eAppendix 4: DEFINITIVE TREATMENT AND ANTIMICROBIAL STEWARDSHIP

An overview of findings relating to definitive treatment can be found in Table 4 in the main manuscript.

Q18: What is considered "treatment failure" of a urinary tract infection and are there host-related risk factors that may influence the risk of treatment failure?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

There is no agreed upon universal definition of treatment failure. In general, treatment failure may result from clinical failure, microbiological failure, or a combination thereof. . Current FDA guidance suggests a composite endpoint that includes both clinical and microbiological responses. The true implications of the combination of clinical cure with microbiologic failure at follow-up remains uncertain. An analysis of individual participant data from several phase III studies found an increased risk of "late clinical failure" in patients with clinical cure but microbiological persistence[266], but this phenomenon is often difficult to distinguish from a new infection.Notably, in two recent large RCTs, positive urine cultures at follow up in patients who had resolved clinical signs and symptoms of infection did not appear to predict a higher risk of relapse of infection within the follow-up period.[114,267] Commonly identified epidemiologic risk factors for treatment failure identified in observational studies include older age, diagnosis of diabetes, presentation with septic shock, pregnancy, and immunosuppression.[268–279] No compelling data exist to support adjusting urinary tract infection treatment based on the potential risk factors for treatment failure that have been identified in these retrospective studies.

Overall summary

Definitions of treatment failure and potential host-related risk factors for treatment failure

There is no agreed upon universal definition of treatment failure and identified potential contributing factors vary widely between studies. In general, a definition of treatment failure can include clinical failure (such as failure of the initial urinary symptoms to resolve or recurrent urinary symptoms prior to the end of the specified observation period with or without a decision to repeat treatment), microbiological failure (such as a positive urine culture with or without urinary symptoms following treatment), or a combination thereof (sometimes referred to as a "responder" endpoint). The FDA considers a "responder" endpoint as indicative of clinical efficacy. The responder endpoint for both uncomplicated and complicated UTI include both clinical and microbiologic response. It should be noted that the FDA suggests a reduction of a bacterial pathogen to fewer than 10^3 CFU/mL in the urine as a threshold for microbiologic success. Failure to meet the definition of "clinical and microbiologic response" (however that may be defined in any given study), would be considered treatment failure. Similarly, the EMA guidance on evaluation of medicinal products for treatment of uncomplicated UTI suggests a composite primary endpoint consisting of both clinical and microbiological success. In most published studies, death from any cause is considered "treatment failure" and those deaths could

be inappropriately attributed to either group in a comparative study and distort the association between exposure and outcome. Table 7 demonstrates how heterogeneous study definitions of treatment failure can be.

A study analyzing data from 13 phase 3 clinical trials found that discordant clinical and microbiological outcomes at the test of cure visit were associated with an increased risk of late clinical failure, highlighting that microbiological outcomes may have a role in assessing treatment success for complicated urinary tract infections.[266] However, there conflicting data and a paucity of high quality evidence showing that persistence of urine culture positivity after resolution of symptoms results in an increased risk of future relapse. Two recent, large randomized controlled trials, one in children and one in adults, demonstrated a higher rate of follow up culture positivity in patients receiving shorter course therapies, but this increased rate of follow up culture positivity did not result in a higher risk of relapsed infection.[114,267] Thus, there is no current role for the routine use of follow up urine cultures establishing treatment failure in patients whose symptoms have resolved.

It should be noted that there is insufficient high-quality evidence to inform whether or not one type of endpoint can be used as a surrogate to predict the other (e.g., it is unclear if microbiological success can be used as a surrogate for clinical success). The relevance of asymptomatic microbiologic "failure" of treatment is not well understood. The dogmatic teaching by many clinicians that urine is "sterile" has led to many questions surrounding the significance of asymptomatic bacteriuria (discussed in section 2 of this manuscript) and the presence of bacteriuria shortly following treatment with antimicrobials, especially in the context of clinical symptom resolution. Advances in technology have allowed the decades old mantra about the sterility of urine to be disproven; groundbreaking studies in the early 2010s used metagenomic technology to demonstrate that the urine of even healthy humans is not sterile.[169–172] Subsequently, several studies have attempted to develop a taxonomic profile of the human genitourinary tract microbiome using 16S ribosomal RNA and metagenomic sequencing.[169,171,173,280] These studies demonstrate high inter-person variability in urinary microbiota composition, highlighting that there is no clear microbiome "state" that can be used to infer the distinction between asymptomatic bacteriuria and symptomatic UTI.[281–285] Additionally, many of these studies demonstrate significant overlap in the microbial profile of patients with urinary disorders such as recurrent UTIs in both the asymptomatic and symptomatic states.[281,286,287] While direct application of this science to clinical practice is still in its infancy, the complexity of the urinary microbiome has clear ramifications for the definitions relevant to clinical care, such as asymptomatic bacteriuria and microbiologic failure.

Observational studies in a variety of populations (see Table 6) have identified several potential host-related risk factors that are associated with risk of treatment failure, however most of these studies are retrospective, of limited sample and/or effect size, and rely on multivariate analyses to identify potential associations between exposures and outcomes. No single characteristic has been consistently identified as a risk factor for treatment failure across all studies. Many potential risk factors were found to be associated with treatment failure in some studies, but not others, highlighting the challenges of establishing causality through observational study. Additionally, substantial variation in outcomes exist owing to the review above describing that no commonly accepted definition of treatment failure exists. While a particular risk factor for

treatment failure may have been identified in retrospective studies, there are often conflicting findings in prospective studies in populations with those same risk factors. For example, older age has been consistently identified in observational studies as a possible risk factor for treatment failure, however a Cochrane review of RCTs in cystitis found (in 4 of those RCTs) no difference in short-term (less than 2 weeks post-treatment) persistent UTI (RR = 0.85 [95% CI: 0.29 to 2.46]) or clinical failure (RR = 0.98 [95% CI: 0.62 to 1.54]) between "short" (3 to 6 days) and "long" (7 to 14 days) antibiotic courses.[288] This provides evidence that older adults could be treated with similar antibiotic courses as younger patients.

The most identified epidemiologic risk factors for treatment failure identified in existing literature are described in Table 6 below:

Table 6. Commonly identified potential risk factors for treatment failure in published retrospective, observational studies.

Possible risk factor for treatment failure	Studies finding a positive association between the risk factor and treatment failure
Older age (heterogeneous definitions)	Lawrenson et al.[268](2001), Efstathiou et al.[269](2003), Karve et al.[271](2017), Rosa et al.[289](2017), Jorgensen et al.[273](2018), Pujades-Rodriguez et al.[274](2019), Eliakim-Raz et al.[275](2019), Martischang et al.[276](2021), Trautner et al.[277](2022), Dunne et al.[278](2022)
Diabetes (heterogenous severity)	Lawrenson et al.[268](2001), Efstathiou et al.[269](2003), Pertel et al.[270](2006), Lamas Ferrerio et al.[279](2017), Dunne et al.[278](2022)
Septic shock at time of presentation	Efstathiou et al.[269](2003), Jorgensen et al.[273](2018), Eliakim-Raz et al.[275](2019)
Pregnancy	Lawrenson et al.[268](2001), Jorgensen et al.[273](2018)
Immunosuppression (heterogenous definitions)	Efstathiou et al.[269](2003), Eliakim-Raz et al.[275](2019)
Other potential risk factors with less strong associations with treatment failure that have been identified in the studies above include: recent receipt of antibiotics, "bedridden" status, presence of catheters, adequacy of initial treatment, intensive care unit admission, dementia, psychiatric disorders, bacteremia, resistant organisms, male biological sex, and prior hospitalization.	

Table 7. Heterogeneous definition(s) of treatment failure in published studies in UTI.	
Study (*in chronological order*)	**Definition(s) of treatment failure**
RANDOMIZED CONTROLLED TRIALS	
Note the differences in the definitions of clinical or microbiological success or failure used in the many RCTs reviewed in the subsequent questions of this section.	
OBSERVATIONAL STUDIES	
Lawrenson et al.[268] (2001)	• Receipt of a further prescription for an antibiotic within 28 days of initial prescription (clinical)
Efstathiou et al.[269] (2003)	Either: • Identification of bacteria resistant to trimethoprim/sulfamethoxazole, ampicillin/sulbactam, amoxicillin/clavulanate, or fluoroquinolones (microbiological) • Prolonged hospitalization of 10 days or longer (clinical) • Death due to acute pyelonephritis (clinical)
Pertel et al.[270](2006)	Either: • Persistence or reappearance of symptoms or signs of infection by the test-of-cure visit, such that additional antimicrobial therapy was required (clinical) • Urine culture obtained at test-of-cure visit grew $\geq 10^4$ of the original uropathogen (microbiological)
Rosa et al.[289](2017)	• Treatment with an agent reported to be intermediate or resistant against the isolated strain of *E. coli* (microbiological)
Karve et al.[271](2017)	Either: • Discontinuation of initial antibiotic regimen for reasons other than cure/improvement in symptoms (e.g., dose increases or change in antibiotic) (clinical) • In-hospital death (any cause) (clinical) • Readmission due to recurrence of same infection within 30 days of discharge (clinical)
Jorgensen et al.[273](2018)	• Return visits to the emergency department within 30 days (clinical)
Pujades-Rodgriguez et al.[274](2019)	• Antibiotic re-prescription within 28 days (clinical)
Eliakim-Raz et al.[275](2019)	Either:

	• Signs or symptoms that have not improved by day 5-7 of appropriate therapy (clinical) • New urinary symptoms that have developed within 30 days of the original diagnosis (clinical) • Urine culture taken within 30 days of the original diagnosis at any point in time that grew $\geq 10^4$ of the original uropathogen (microbiological) • Death (any cause) within 30 days of original diagnosis (clinical)
Martischang et al.[276](2021)	Either: • Need for additional or change in antibiotic treatment due to a UTI or lack of efficacy within 28 days following completed initial treatment (clinical) • Bacteriuria with $\geq 10^3$ of the original uropathogen at 14 and 28 days following completed initial treatment (microbiological)
Trautner et al.[277](2022)	Either: • Dispensing of new antimicrobial (clinical) • All-cause hospitalization (clinical) • All-cause outpatient emergency department or clinic visits (clinical)
Dunne et al.[278](2022)	Either: • Receipt of subsequent antibiotic prescription within 28 days of initial prescription (clinical) • UTI-related hospital admission within 28 days of initial prescription (clinical)

Q19: What is the appropriate duration of treatment of acute cystitis in pediatric patients over 2 months of age?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

Based on several randomized trials, shorter courses (3 to 5 days, depending on the antimicrobial used) likely result in comparable outcomes to longer courses (7 to 14 days) and are reasonable for the treatment of cystitis in children older than 2 months when the likelihood of pyelonephritis is deemed to be low.[290–292] Small study size, heterogeneity in trial design (various durations, various antibiotics), endpoint definitions (with frequent use of positive culture at follow up defining treatment failure), and outcomes, preclude a clear recommendation for duration of treatment. Several observational studies suggest that a single parenteral dose of an aminoglycoside may be a reasonable alternative treatment option.[230] No data exists to suggest that initial (or any) parenteral treatment for cystitis is necessary in patients who can tolerate oral treatment.

Overall summary

The appropriate duration of treatment appears to be heavily influenced by the unique pharmacokinetic and pharmacodynamic properties of various classes of antimicrobial agents.

Duration of treatment

Single dose

In a 2012 Cochrane review that included 16 RCTs, a total of 6 studies were used to analyze outcomes when a single dose of treatment was used in comparison to (at the time) a "conventional" 10-day treatment regimen. Statistically significantly higher rates of persistent bacteriuria after completion of treatment were seen in the single dose group compared with the 10-day group (6 studies: RR = 2.01 [95% CI: 1.06 to 3.8]). The significance of a higher rate of persistent bacteriuria is generally unknown, however in children for whom confirmation of symptoms is not possible, it may be a concern.

Unfortunately, only 3 studies comparing a single dose to a 10-day treatment course evaluated clinical outcomes, and often not the same outcomes. One RCT of 30 adolescents aged 12 to 18 saw fewer persistent symptoms reported in the single dose group that received one dose of 3 grams of oral amoxicillin compared with the 10-day duration group that received 250 mg three times daily (1 study: RR = 0.29 [95% CI: 0.03 to 2.5]). Two additional RCTs evaluated the risk of UTI recurrence and found a non-statistically significant higher risk of recurrence in the single dose group (2 studies: RR = 1.38 [95% CI: 0.55 to 3.5]). One of these studies compared a single dose of amoxicillin with 10 days of amoxicillin while the other compared a single dose of amikacin with 10 days of sulfisoxazole. In the context of comparing a single dose to a 10-day course, the studies that used only amoxicillin appear to have comparable outcomes to those that utilized other types of antimicrobials, at least when it comes to persistent bacteriuria (4 amoxicillin studies: RR = 1.97 [95% CI: 0.9 to 4.33] and 2 "other antibiotic" studies: RR = 2.09 [95% CI: 0.71 to 6.18]). Thus, single dose oral therapy may be used in some circumstances, but caution is warranted regarding the potential for failure to eradicate bacteria, particularly for children that cannot express symptoms. Clearly the limited quantity and quality of existing data limits conclusions that can be made.

Several observational studies have evaluated clinical outcomes in children receiving single dose aminoglycosides for treatment of cystitis in pediatric patients ranging from 2 weeks to 18 years old.[230] In fact, 7 of 13 (54%) studies evaluating the use of single dose aminoglycosides for cystitis included in the review consisted only of children. One additional large study reported a mixed population that included children.[293] These studies consistently demonstrate high microbiologic cure rates of 87 to 100%, however only 2 included studies provided clinical cure rates[293,294], only one of which included children (overall clinical cure rate = 83%).[293]

Short vs. long duration.

Several small RCTs directly comparing a single dose versus multiple day treatments of the same antimicrobial consistently demonstrate that a single dose of oral treatment is not sufficient for treatment of cystitis in children.[295–301] A 2002 meta-analysis published by Keren and Chan[302]

demonstrated a consistent trend of increased risk for treatment failure with short course therapy (defined as 3 or less days, including single doses) as compared to long (defined as 7-10 days) with a pooled RR = 1.94 (95% CI: 1.19 to 3.15). A year later, a more systematic and rigorous review was published by the Cochrane Library that provides a more comprehensive and useful assessment of the literature available at that time. Notably, the 2003 Cochrane review excluded single dose studies and included 10 RCTs (quasi-experimental studies were allowed, but none were identified) that compared short (2-4 days) versus standard (7-10 days) durations of therapy for treatment of lower urinary tract infection (UTI) in children aged 3 months to 18 years.[290] The 4 studies that were excluded from this analysis include Helin (1984)[303] and Khan (1981)[304] compared different antibiotics in the short and standard duration groups, McCracken (1981)[305] compared one day treatment with 10 days of treatment, and Tambic (1992)[306] had unbalanced groups with significantly more patients in the 7-day group reporting pyelonephritis compared with the 3-day group. Neither the random nor fixed effects meta-analysis found a statistical difference between the two groups in terms of UTI at the end of treatment (defined as presence of bacteriuria 0 to 10 days after completing treatment, 8 studies: RR = 1.06 [95% CI: 0.64 to 1.76]), recurrent UTI at 1 to 15 months after treatment (10 studies: RR = 0.95 [95% CI: 0.7 to 1.29]), or long-term follow up (10 studies: RR 1.01 [95% CI: 0.77 to 1.33]). Only a singular trial within this meta-analysis evaluated treatment durations as short as 2 days and all included pediatric patients were aged 2-11 years.[307] Thus, we cannot provide a clear recommendation for a 2 day duration of therapy for cystitis treatment.

It should be noted that most of the RCTs (5 studies) in the meta-analysis used sulfonamide containing antibiotics while the others used other antibiotics (most commonly, β lactams or nitrofurantoin). The risk ratio for short compared with standard duration was comparable for studies only containing sulfonamide containing antibiotics (RR = 0.96 [95% CI: 0.64 to 1.44]) and those containing other antibiotics such as β lactams or nitrofurantoin (RR = 0.93 [95% CI: 0.53 to 1.61]). Also of note, one of the RCTs included[308] featured a 3-day pivmecillinam (a "urinary" β lactam) arm and was excluded from the Cochrane review since there was no standard duration comparator; the 3-day pivmecillinam arm had similar rates of microbiologic cure (termed "no significant growth after treatment" in the study) compared with the 3-day sulfamethoxazole and 10-day sulfamethoxazole groups (74% vs. 77% vs. 81%, respectively).

Another Cochrane review published in 2012 adds to the data presented above, but only up to four studies were able to be used in the analyses evaluating short (3-7 days) versus long (10-14 days) of treatment.[291] Notably, these analyses included two of the studies excluded from the 2003 Cochrane review.[303,304] These smaller analyses found no statistical difference using a random effects model in UTI recurrence (4 studies: RR = 1.25 [95% CI: 0.74 to 2.13]), re-infection (2 studies: RR = 0.88 [95% CI: 0.44 to 1.74]), or persistent bacteriuria (3 studies: RR = 1.09 [95% CI: 0.67 to 1.76]).

More recently in 2024, a systematic review and meta-analysis was published that evaluated treatment failure (defined as a positive urine culture test after treatment) as the primary outcome.[292] This study included 17 RCTs totaling 1,666 patients (mean ages ranged from 4.2 to 7.8 years). Notably, these authors dichotomized the treatment durations for the sake of comparison into "short-course" therapy (less than 5 days, including single dose regimens) and "longer-course" therapy (7 to 10 days). There were some RCTs in the 2012 Cochrane review that

allowed comparison of single dose to "short course" therapy (defined as a duration of 3 to 7 days). Notably, the differences in UTI recurrence (2 studies, RR = 1.5 [95% CI: 0.43 to 5.26]) and persistent bacteriuria (2 studies: RR = 1.3 [95% CI: 0.65 to 2.62]) were less pronounced (e.g., not statistically significant) than when comparing single dose regimens to longer treatment durations (such as 10 days), but it is not possible to definitively say that a single dose is comparable in terms of these outcomes compared to "short courses" given there are only 2 studies of limited size and power. As such, including single dose regimens, already shown to likely be worse than 10 day regimens with respect to bacterial eradication, in the same group as 3 to 5 day regimens may fail to account for any potential differences in the effectiveness of 3 to 5 day durations as compared to single dose durations. Given the fact that the single dose regimens were included in this "short course" bucket, it is not surprising that this SRMA favors longer course treatment. Further rigorous study of short (but not single dose) regimens of antimicrobials used to treat UTI in children in comparison to "conventional" longer treatment durations is still needed.

A recent placebo-controlled randomized non-inferiority (NI margin = 5%) clinical trial (SCOUT) attempted to address duration of therapy in children with UTI.[267] The trial enrolled 664 children aged 2 months to 10 years to either "standard" course (10 days) or "short" course (5 days) of treatment for their UTI. This investigation did not differentiate between the clinical syndromes of cystitis and pyelonephritis in the primary outcome analysis, however the distinction between cystitis and pyelonephritis can be difficult to make in clinical practice, given younger children are often unable to self-report urinary symptoms. In this study, 38% of children had a fever at the time of presentation. The primary outcome, termed "treatment failure", was defined as occurrence of UTI (defined as the presence of all of the following criteria: (1) 1 or more signs or symptoms of UTI such as fever ≥ 38C, suprapubic, abdominal, or flank pain, urinary urgency, frequency, or hesitancy, dysuria in children 2 years and older, poor feeding or vomiting in children under 2 years old; and (2) pyuria defined as 10 or more WBCs per mm^3 or 5 or more WBCs per HPF or leukocyte esterase more than or equal to trace on dipstick urinalysis; and (3) a positive urine culture defined by growth of a single uropathogen at counts of 5 x 10^4 or higher CFU/mL from a catheterized specimen or 10^5 or higher CFU/mL from a clean voided specimen) between day 6 and the day 11 to 14 visit. This meant that patients in the short course group would have a longer follow-up time to experience failure while off antibiotics (up to 8 days) as compared to the standard course group (up to 4 days). Furthermore, follow up urine cultures were obtained in patients during the period of antibiotic (continued therapy in the longer course arm) vs. not (short course arm had stopped therapy), creating a significant risk of bias as it is expected that urine cultures would be less likely to grow in patients still taking antibiotics than those not. Secondary outcomes included symptomatic UTI after the day 11 to 14 visit with follow-up ending on day 38 to 44. Treatment failure was more common in the short course group (4.2%) versus the standard course group (0.6%) and the upper bound of the one-sided 95% confidence interval was 5.5%, which did not meet the prespecified 5% margin for non-inferiority. However, there was no significant difference in patients with persistent symptoms between the two arms; the treatment failure difference was driven by positive urine cultures. In a post hoc analysis for this guideline, it appears that overall rates of failure between days 6 and 38 to 44 were 8% (27 of 336) in the short course group compared with 4.3% (14 of 328) in the standard course group. This yields a risk difference of 3.7% with an upper bound of the one-sided 95% confidence interval being 6.8%. Nonetheless, the authors concluded that short course

therapy is reasonable for children aged 2 months to 10 years given the overall extremely low incidence of treatment failure. There are concerns of several types of bias in the study, as patients were more likely to "fail" treatment by growing bacteria in the urine during the period of placebo vs. antibiotic randomization, which was defined as a new UTI during that period. There was no difference in rates of clinical symptom resolution in both arms, and there was no difference in subsequent relapse of infection. Taken together, it is possible that it is simply easier to culture bacteria from urine when asymptomatic patients are receiving placebo, rather than antibiotics.

A second multicenter, noninferiority (NI margin = 5%), investigator-initiated, randomized, controlled trial (STOP) evaluated the impact of treatment duration in children with febrile UTI. The trial randomized 142 children aged 3 months to 5 years to either "standard" course (10 days) or "short" course (5 days) of amoxicillin/clavulanate for treatment of febrile UTI, including pyelonephritis. Patients were excluded if they had complicated febrile UTI (i.e., fever persisting >48 hours following commencement of treatment and/or need to change the antibiotic, dehydration, or vomiting), presence of urinary catheter, were immunocompromised, received antibiotic therapy within preceding 15 days, and patients with concern for underlying intestinal malabsorption. The primary endpoint, symptomatic UTI recurrence within 30 days following completion of therapy was noted to be 2.8% in the 5-day cohort versus 14.3% in the 10-day cohort with absolute difference of 11.51% (95%CI –20.54% to –2.4%). Secondary endpoints included clinical recovery at the end of treatment (defined as complete resolution of fever and other signs/symptoms of infection), adverse events, and development of antimicrobial resistance. Resolution of signs and symptoms was higher in the 5-day group (97.2%) when compared to the 10-day group (92.9%), but was not statistically different (p =0.27). The need for administration of further antibiotic therapy at the second follow-up after 30 days was not statistically different in the 5-day group (1.4%) when compared to the 10-day group (8.6%) (p = 0.06).

Collectively, numerous studies have suggested that shorter durations of therapy are likely effective in treating cystitis in children. However, there are heterogeneity in trial design (various durations, various antibiotics), endpoint definitions (with frequent use of positive culture at follow up defining treatment failure), and outcomes, precluding a clear recommendation.

Route of administration

We were unable to find data that has demonstrated a benefit of initial parenteral therapy for pediatric patients with cystitis who are able to tolerate oral therapy and it seems reasonable that an attempt should be made to convert parenteral therapy to oral as soon as able.[309]

Q20: What is the appropriate duration of treatment of acute pyelonephritis in pediatric patients >2 months of age?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

Available randomized trial data are inadequate to provide a clear recommendation on the optimal duration of treatment for acute pyelonephritis in children over 2 months of age.[267,310,311] Most

existing data suggest similarly high rates of clinical success when patients receive 5 to 9 days (depending on the antimicrobial used) when compared to 10 to 14 days total.[312,313]

Overall summary

Duration of treatment

A 2014 Cochrane review failed to identify the optimal length of treatment in children with pyelonephritis based on three included RCTs (totaling 283 children) and specifically identified studying shorter treatment durations as an area for future research.[310] As mentioned above, although the recent randomized SCOUT trial included pediatric patients with pyelonephritis, there were several limitations that make the results challenging to contextualize. Clinical success rates were very high with the short-course regimen in that study.[267] Additionally, it is likely that some children with pyelonephritis were included in the STOP trial [311] which demonstrated non-inferiority of a 5-day treatment regimen compared with 10 days. The authors of this guideline again recognize the challenges in differentiating cystitis and pyelonephritis in children and it is reasonable to assume that the populations in both studies were mixed, including both patients with cystitis and pyelonephritis. Retrospective studies evaluating treatment outcomes in pediatric patients treated for acute pyelonephritis have demonstrated similar efficacy between short (6 to 9 days) compared with long (10 to 14 days) durations of treatment (OR for treatment failure within 30 days of completing antibiotic treatment, short vs. long = 1.22 [95% CI: 0.75 to 1.98]).[312] A retrospective cohort analysis of a large administrative claims database (Truven Health MarketScan) was published by Afolabi et al. in 2020 and evaluated the association of antibiotic treatment duration with recurrence rates in children aged 2 to 17 years with new-onset cystitis or pyelonephritis.[313] A total of 7,698 patients were included, however only a small proportion of those enrolled were diagnosed with pyelonephritis (14.3%). For adjustment for several covariates, the 7-day treatment duration was not statistically significantly associated with an increased odds of recurrence (which included either relapse or reinfection) when compared to the 10-day (OR = 1.07 [95% CI: 0.85 to 1.33]) or 14-day (OR = 0.89 [95% CI: 0.45 to 1.78]) treatment groups. There were proportionally fewer relapses in the 7-day treatment group (5.4%) as compared to the 10-day (6.3%) and 14-day (7.1%) groups, however this included patients who did not have pyelonephritis at the time of diagnosis. Confounding by indication may explain these differences as it is likely reasonable to assume that patients with pyelonephritis at time of diagnosis are more likely to be prescribed 10 days or more of treatment based on historical practices. This hypothesis is further supported by the fact that recurrence was more common in those patients who had pyelonephritis at time of diagnosis (9.9%) compared with those with just cystitis (4.8%).

Route of administration

Four RCTs[314–317] (totaling 1,131 children) that were included in the aforementioned 2014 Cochrane review[310] demonstrated that oral therapy alone (for 10 to 14 days) was as effective as sequential IV therapy (for 3 to 4 days) followed by oral therapy to finish the course of treatment with regard to prevention of persistent kidney damage at 6 to 12 months in children with pyelonephritis (4 studies, 943 patients: RR = 0.82 [95% CI: 0.59 to 1.12]). When limiting the

included patients to those with kidney parenchymal damage on initial dimercaptosuccinic acid (DMSA) scintigraphy, oral therapy remained at least as effective as sequential IV to oral therapy (4 studies, 681 patients: RR = 0.79 [95% CI: 0.61 to 1.03]). The number of patients with persistent UTI at 72 hours after starting treatment did not differ between groups (2 studies, 542 patients: RR = 1.10 [95% CI: 0.07 to 17.41]). Only one study (Hoberman 1999)[315] reported rates of recurrent bacteriuria and symptomatic UTI (within 6 months); there were no differences between the oral only and sequential treatment groups in either of those outcomes (recurrent bacteriuria: RR = 0.65 [95% CI: 0.28 to 1.51] and symptomatic UTI within 6 months: RR = 0.67 [95% CI: 0.27 to 1.67]).

Likewise, six RCTs[318–323] (totaling 917 children) compared oral treatment after 3 to 4 days of IV treatment with a long, IV-only course of treatment of 7 to 14 days in duration. There was no difference between groups for recurrent UTI within 6 months (5 studies, 993 patients: RR = 0.97 [95% CI: 0.58 to 1.62]) nor persistent bacteriuria at the end of treatment (4 studies, 305 patients: RR = 0.78 [95% CI: 0.24 to 2.55]).

The totality of the evidence suggests that entirely oral treatment regimens achieve similar outcomes to IV followed by oral treatment regimens and IV-only treatment regimens and supports the practice of utilizing oral treatment options when the patient can reliably absorb and tolerate the oral antimicrobial.

Q21: What is the appropriate duration of treatment for acute cystitis in adults?

Executive summary

Based on the totality of the evidence available, we can provide clear recommendations on the optimal durations of treatment for cystitis (regardless of biological sex) for the antimicrobial classes listed below:

- Nitrofurantoin: 5 days[324–326]
- Trimethoprim/sulfamethoxazole: 3 days[325,327,328]
- Fluoroquinolones: 3 days[325,329–334]
- Oral fosfomycin: single dose[214,335–343]
- Pivmecillinam: 3 days[325,344–348]
- Gepotidacin: 5 days[349]

Data are insufficient to enable clear recommendations for duration of treatment for other potential treatment options including β lactams and parenteral aminoglycosides. Some pediatric data support a 5-day treatment duration when oral beta-lactams are used to treat cystitis.[311]

Overall summary

Nitrofurantoin

One randomized controlled trial evaluated 3 days of nitrofurantoin (NTF) versus placebo in the treatment of acute cystitis in symptomatic, adult, non-pregnant women, aged 15 to 54 years old with pyuria as determined by a positive leukocyte esterase test.[326] 70 women were included in the analysis on day 3. On day 3, 13 of 35 (37%) women in the nitrofurantoin group and 7 of 35 (20%) women in the placebo group reported symptomatic cure ($p = 0.08$). A total of 67 women were included in the analysis at day 7. On day 7, 24 of 34 (70%) women in the nitrofurantoin group and 14 of 33 (42%) women in the placebo group reported symptomatic cure ($p = 0.003$). At inclusion, 56 women had bacteriuria of $\geq 10^5$ CFU/mL. Of these women, significantly more patients in the nitrofurantoin group achieved bacteriologic cure at day 3 (81% vs. 20%, $p < 0.001$) and day 7 (74% vs. 41%, $p = 0.05$). In a network meta-analysis published in 2020[325], there was no statistically significant difference between the effects of the 5-day and 3-day regimens for clinical response (RR = 1.29 [95% CrI: 0.71 to 2.24]) or microbiologic response (RR = 1.745 [95% CrI: 0.96 to 3.66]), however the quality of evidence was very low and lower observed clinical and microbiologic cure rates may be clinically significant. Based on our review and published meta-analyses[324,325], studies with the highest internal validity appear to suggest that giving nitrofurantoin for 5- or 7-days results in similar clinical outcomes (RR = 0.99 [95% CI: 0.96 to 1.02]). There may be a slight advantage to other therapeutic options from a microbiologic perspective regardless of the duration of nitrofurantoin given (RR = 0.93 [95% CI: 0.89 to 0.97]), but as previously mentioned, the clinical significance of this issue is questionable.

Table 8 below demonstrates that many of the early RCTs that lead to FDA approval of uncomplicated urinary tract infections primarily featured a 7-day duration.

Table 8. Clinical and microbiological outcomes of RCTs evaluating different nitrofurantoin regimens for cystitis.

RCT (grouped by duration of NTF treatment)	Nitrofurantoin dosing	Nitrofurantoin duration	Clinical cure (specified time point)	Microbiologic cure (specified time point)
Hooton et al.[223](1995)	100 mg four times daily	3 days	61% (4-6 weeks)	84% (day 4-6)
Christiaens et al.[326](2002)	100 mg four times daily	3 days	37% (day 3) 70% (day 7)	81% (day 3) 74% (day 7)
Gupta et al.[350](2007)	100 mg twice daily	5 days	90% (day 5 to 9) 84% (day 30)	92% (day 5 to 9)
Huttner et al.[214](2018)	100 mg three times daily	5 days	75% (day 14) 70% (day 28)	82% (day 14) 74% (day 28)
Van Pienbroeck et al.[351](1993)	50 mg four times daily	7 days	82% (day 42)	87% (day 42)
Spencer et al.[352](1994)	100 mg twice daily	7 days	87.2% (day 9-15)	82.3% (day 9-15)
Iravani et al.[353](1999)	100 mg three times daily	7 days	93% (day 4-10)	86% (day 4-10)

			89% (4-6 weeks)	82% (4-6 weeks)
Stein et al.[354](1999)	100 mg once daily	7 days	91.7% (day 32)	91.1% (day 32)
Ernst et al.[355](2005)	100 mg twice daily	7 days	87% (day 28)	n/a

β-lactams, excluding pivmecillinam

Single dose. Multiple randomized trials have evaluated single dose regimens of various β-lactams.

Table 9. Clinical and microbiological outcomes of RCTs evaluating single dose regimens of various β lactams for cystitis.

RCT (grouped by duration of treatment)	β-lactam	Dosing regimen (all single dose)	Clinical cure (specified time point)	Microbiologic cure (specified time point)
Greenberg et al.[356](1986)	Cefadroxil	1 gram once	47% (within 3 days) 25% (4 weeks)	
Asbach et al.[357](1991)	Cefixime	400 mg once	89.4% (14 to 17 days)	
Raz et al.[358](1991)	Amoxicillin/clavulanate	3 grams/125 mg once	78.1% (7 days) 67.2% (4 weeks)	70.9% (7 days) 65.5% (4 weeks)
Masterton and Bochsler[359](1995)	Amoxicillin/clavulanate	3 grams/250 mg once	83.3% (7 days) 73.8% (6 weeks)	76.4% (7 days) 64.1% (6 weeks)

A small RCT conducted in female outpatients aged 18 to 35 years with symptoms of acute cystitis received a single dose of 400 mg of cefixime.[[357]] 17 of 19 patients (89.4%) who received the single dose of cefixime had both eradication of bacteriuria and resolution of clinicals symptoms (termed "responders") at follow-up 14 to 17 days after treatment. All 19 patients who received cefixime had a pre-treatment urine culture that grew *Escherichia coli* (17 patients) or *Proteus mirabilis* (2 patients).

An arm of the 1986 RCT by Greenberg et al.[[356]] featured a single 1 gram dose of cefadroxil which only led to a 47% bacteriologic cure within 3 days after finishing treatment and a 25% bacteriologic cure at 4-week follow-up. The majority of the "not cured" cases represented relapses (negative culture within 3 days of finishing treatment, but a subsequent culture at a follow-up visit was positive for the same initial uropathogen at 2- or 4-weeks post treatment) or failures (positive culture with the initial uropathogen within 3 days of finishing treatment); only 1 patient had reinfection (positive culture with uropathogen different than the pre-treatment organism). The authors report that all of the bacteriologic failures and relapses were also

symptomatic. The vast majority of the pathogens in this study were *E. coli* (99 of 122 isolates) and were only 65% susceptible to cephalothin, though notably, it is not a reliable predictor of cefadroxil susceptibility.[226]

A placebo-controlled randomized trial by Raz et al. (1991)[358] included 55 women who received a single dose of 3.125 grams (3 grams of amoxicillin, 125 mg clavulanic acid) followed by placebo caplets every 8 hours for 3 days (as the comparator group was 3-days of amoxicillin/clavulanate). Clinical cure at 7 days and 4 weeks post-treatment was 78.1% and 67.2%, respectively. Microbiologic cure at 7 days and 4 weeks post-treatment was 70.9% and 65.5%, respectively. Interestingly, when stratified by recurrency, women without recurrent UTI at time of randomization had numerically worse clinical and statistically significantly worse microbiologic outcomes at both time points (clinical cure: 86.2% single episode vs. 69.2% recurrent UTI at day 7 and 82.7% single episode vs. 61.5% recurrent UTI at 4 weeks post-treatment; microbiologic cure: 89.7% single episode vs 53.8% recurrent UTI at day 7 [$p < 0.001$] and 86.2% single episode vs. 50% recurrent UTI at 4 weeks post-treatment [$p = 0.07$]).

Another RCT by Masterton and Bochsler (1995)[359] evaluated a single 3.25 gram (3 grams of amoxicillin, 250 mg of clavulanate potassium) dose of amoxicillin/clavulanate for the treatment of acute uncomplicated cystitis in 144 female patients. Clinical success was found to be 83.3% at day 7 post-treatment and 73.8% at day 42 post-treatment. Microbiologic success found to be 76.4% at day 7 post-treatment and 64.1% at day 42 post-treatment. The lower rates of clinical success at day 42 appear primarily driven by an increase in the proportion of patients who experienced clinical relapse (initial resolution, but then return of urinary symptoms). The lower rates of microbiologic success at day 42 appear to be driven primarily by failure (persistence of the original pathogen at $\geq 10^5$ CFU/mL); only 12 of 117 (10.3%) of patients had re-infection with a different pathogen. 117 of 144 (81.3%) of the isolates were *Escherichia coli* and 15 of 144 (10.4%) were *Staphylococcus saprophyticus*.

The totality of evidence suggests that single doses of β-lactams may provide acceptable early clinical and microbiologic response rates, but many clinical relapses and/or bacteriologic failures may occur after the first week post-treatment completion, especially in women with recurrent infections.

3 days. Several randomized trials have investigated 3-day durations of various β-lactams and are reviewed below in brief and in Table 10.

Table 10. Clinical and microbiological outcomes of RCTs evaluating 3-day regimens of various β lactams for cystitis.

RCT	β-lactam	Dosing regimen	Clinical cure	Microbiologic cure

(in chronologic order)		(all for 3 days)	(specified time point)	(specified time point)
Sandberg et al.[360](1985)	Cefadroxil	1 gram once daily	80% (7 days) 75% (5 weeks)	
Greenberg et al.[356](1986)	Cefadroxil	500 mg twice daily	68% (within 3 days) 58% (4 weeks)	
Raz et al.[358](1991)	Amoxicillin/clavulanate	250 mg/125 mg three times daily	87% (7 days) 77.7% (4 weeks)	83.3% (7 days) 75.9% (4 weeks)
Raz et al.[361](1994)	Cefixime	400 mg once daily	89% (7 days) 81% (4 weeks)	83% (7 days) 77% (4 weeks)
Goto et al.[362](1999)	Cefpodoxime proxetil	200 mg once daily	64.3% (end of treatment)	82.1% (end of treatment)
Kavatha et al.[363](2003)	Cefpodoxime proxetil	100 mg twice daily	98.4% (4 to 7 days) 87.3% (28 days)	98.4% (4 to 7 days) 86% (28 days)
Hooton et al.[228](2005)	Amoxicillin/clavulanate	500 mg/125 mg twice daily	58% (2 weeks)	76% (2 weeks)
Hooton et al.[224](2012)	Cefpodoxime proxetil	100 mg twice daily	88% (5 to 9 days) 82% (30 days)	81% (5 to 9 days)
Hamasuna et al.[364](2014)	Faropenem	200 mg three times daily	76.7% (5 to 9 days) 46.2% (4 to 6 weeks)	58.9% (5 to 9 days) 40.4% (4 to 6 weeks)
Sadahira et al.[365](2017)	Cefditoren pivoxil	100 mg three times daily	90.9% (5 to 9 days)	82.5% (7 to 14 days)

Sandberg et al. (1985)[[360]] conducted a 11-center RCT in 3 regions of Sweden which included non-pregnant women older than 15 years of age (mean age = 35.7 years) presenting with symptoms of urinary frequency and dysuria. Patients with a history of recurrent UTI (2 episodes in the last year) were excluded. One of the treatment arms resulted in patients receiving 1 gram of cefadroxil once daily for 3 days. Observed “cure” (defined as both disappearance of symptoms and presence of less than 10^4 CFU/mL of midstream urine) rates were 66 of 82 (80%) patients at 1 week post-treatment and 58 of 77 (75%) patients 5 weeks post-treatment. The majority of infections were due to either *E. coli* (68% of total) or *S. saprophyticus* (27% of total).

Goto et al. (1999)[362] investigated cefpodoxime proxetil in a 200 mg once daily for 3 days dosing regimen for acute uncomplicated cystitis in Japanese women who were at least 16 years old. A total of 31 women were randomized into the cefpodoxime arm and saw initial uropathogens removed (microbiologic success) in 23 of 31 (82.1%) women when evaluated at the end of the 3-day treatment regimen. Although the reported number of women with "excellent" clinical efficacy (an assessment guided by the Japanese UTI Committee that combines subjective symptoms, pyuria, and bacteriuria) was only 64.3% in the cefpodoxime group, this was similar to that of the group that received ciprofloxacin 200 mg twice daily for 3 days (63%).

An arm of the 1986 RCT by Greenberg et al.[356] featured a 3-day course of cefadroxil 500 mg twice daily which resulted in a 68% bacteriologic cure within 3 days of finishing treatment and 58% bacteriologic cure at 4-week follow-up. Similar to what was seen in the single dose cefadroxil arm of this trial, most of the patients who did not achieve cure at either follow-up time point were due to relapses (negative culture within 3 days of finishing treatment, but a subsequent culture at a follow-up visit was positive for the same initial uropathogen at 2- or 4-weeks post treatment) or failures (positive culture with the initial uropathogen within 3 days of finishing treatment); only 1 patient had reinfection (positive culture with uropathogen different than the pre-treatment organism). The authors report that all the bacteriologic failures and relapses were also symptomatic (clinical failures).

Hooton et al. (2005)[228] published an RCT in which one of the comparators was a 3-day course of amoxicillin/clavulanate dosed 500 mg/125 mg twice daily. The study population The rate of clinical cure (defined as the absence of symptomatic persistent or recurrent UTI) in the amoxicillin/clavulanate group was only achieved in 93 of 160 (58%) of women when assessed at the 2-week included women aged 18 to 45 years old with symptoms consistent with acute uncomplicated cystitis and a urine culture with at least 10^2 CFU/mL from the University of Washington Student Health Center and at Group Health Cooperative. post-treatment follow-up visit. Microbiological cure was also inferior in the amoxicillin/clavulanate group and was achieved in 118 of 156 (76%) of women when assessed at the 2-week post-treatment visit. A total of 109 women in the amoxicillin/clavulanate group had uropathogen(s) that was/were susceptible to the treatment antibiotic. Although there was a trend toward better clinically oriented outcome (being free of symptoms) in women treated with amoxicillin/clavulanate when the organism was susceptible, there was not a statistically significant difference in the outcomes between those with susceptible vs. non-susceptible isolates ($p = 0.17$). Of the 67 persistent or recurrent UTIs in the amoxicillin/clavulanate group, 33 (50%) occurred in the first 2 weeks and 34 (50%) occurred in weeks 3 through 10 following treatment.

Hooton et al. published another RCT years later (2012)[224], this time with cefpodoxime proxetil dosed at 100 mg twice daily for 3 days. The study population consisted of women 18 to 55 years old at an outpatient clinic in Seattle, WA and clinical research clinic in Miami, FL who were in "good general health", with symptoms consistent with acute cystitis and pyuria (defined as WBC ≥ 8 cells/mm^3). The primary outcome of this study was overall clinical cure at the 30-day follow-up visit (defined as not requiring further antimicrobial treatment). In the intention-to-treat population (assuming that those lost to follow-up experienced clinical cure), overall clinical cure was found in 123 of 150 (82%) patients in the cefpodoxime group; this did not differ

significantly from the per-protocol population (106 of 133 patients, 80%). Early clinical cure and early microbiologic cure were assessed at the follow-up visit that took place 5 to 9 days after completion of treatment. Early clinical cure was seen in 132 of 150 (88%) patients in the cefpodoxime group. Early microbiologic cure was seen in 104 of 129 (81%) patients in the cefpodoxime group.

Kavatha et al. published a multi-center RCT from four medical centers throughout the metropolitan area surrounding Athens, Greece in 2003.[363] The study population included women between 18 and 70 years old referred to relevant outpatient clinics due to symptoms consistent with acute cystitis. One of the comparators in this study was a 3-day course of cefpodoxime proxetil 100 mg twice daily. Of the 63 women who received cefpodoxime that were included in the final analysis, 62 (98.4%) reported clinical cure (defined as free from all symptoms) at the first follow-up visit (at 4 to 7 days after completion of treatment) and 48 of 55 (87.3%) women who attended the second follow-up appointment (28 days after completion of treatment) reported clinical cure. Bacteriologic cure (defined as eradication of the causative pathogen) was achieved in 62 of 63 (98.4%) patients at the first follow-up visit and in 43 of 50 (86%) patients at the second follow-up visit. The authors report that all patients who failed treatment bacteriologically also had symptoms consistent with cystitis (were also clinical failures). Note that the results of this RCT are much more encouraging than those seen in the other RCT (by Hooton et al., 2012) that evaluated 3-day treatment with cefpodoxime proxetil.

In addition to evaluating a single dose regimen of amoxicillin/clavulanate (as reviewed in the previous section), Raz et al. (1991)[358] also included an arm that received amoxicillin/clavulanate dosed at 250 mg/125 mg every 8 hours (three times daily) for 3 days. Clinical cure was observed in 87% at 7 days post-treatment and in 77.7% at 4 weeks post-treatment. Microbiological cure was observed in 83.3% at 7 days post-treatment and in 75.9% at 4 weeks post-treatment. Like what was seen in the single dose group (and reviewed above), clinical and microbiologic outcomes were numerically better in women who did not have recurrent UTI. The 3-day group performed numerically better than the single dose group in all outcomes at 7 and 28 days post-treatment, however the difference in clinical cure rates was not statistically significant ($p = 0.33$ for 7 days post-treatment and $p = 0.31$ for 28 days post-treatment) while the difference in microbiological cure was at 7 days-post treatment ($p < 0.001$), but not at 28 days post-treatment ($p = 0.07$).

Raz et al. published another RCT in 1994[361] using the extended-spectrum oral cephalosporin cefixime dosed 400 mg once daily for 3 days. The study population included women 16 years or older who had been referred to a single outpatient clinic in Israel with a diagnosis of acute cystitis. Of the 49 women that received cefixime and completed all treatment and follow-up appointments, clinical cure at 7 days post-treatment completion was seen in 44 patients (89%). At the follow-up visit 28 days post-treatment completion, clinical cure was reported in 40 of 49 (81%) patients. Eradication of all microorganisms in the urine (microbiological cure) was seen in 41 of 49 (83%) women at 7 days post-treatment and in 38 of 49 (77%) women at 28 days post-treatment completion. *Escherichia coli* accounted for 81% of all uropathogens in the cefixime group and 8 of the 11 failures or relapses were due to *E. coli*.

In 2014, Hamasuna et al. published a multi-center RCT at 35 sites throughout Japan investigating the use of an oral carbapenem, faropenem, for the treatment of acute cystitis.[364] The study population included women aged 20 years or older (median age = 49.5 years) with any cystitis symptoms with pyuria and bacteriuria. One of the study arms received faropenem 200 mg three times daily for 3 days. The primary endpoint was microbiological efficacy (defined as less than 10^3 CFU/mL after treatment) at 5 to 9 days post-treatment completion. In the intention-to-treat population, microbiological efficacy was 58.9% (43 of 73 patients) in the 3-day faropenem group. At 4 to 6 weeks after treatment completion, the microbiologic efficacy was 40.4% (21 of 52 patients). Clinical efficacy (defined as the absence of symptoms) was 76.7% (56 of 73 patients) at 5 to 9 days post-treatment and 46.2% (24 of 52 patients) at 4 to 6 weeks post-treatment.

More recently (2017), Sadahira et al. published a multi-center RCT at various hospitals or urology clinics within the Okayama prefecture in Japan.[365] The study population included women aged 20 years or older without fever with any symptoms of cystitis. One of the treatment arms received 3 days of cefditoren pivoxil, an oral third generation cephalosporin, dosed at 100 mg three times daily. Clinical and microbiologic efficacies were assessed at the second visit (5 to 9 days after randomization) and the third visit (7 to 14 days after completion of treatment), respectively. The primary outcome of the study was microbiologic efficacy (defined as a negative urine culture; if bacteria were present, they had to be less than 10^3 CFU/mL) 5 to 9 days after the end of administration. The microbiologic efficacy of the 3-day cefditoren group was 82.5% (33 of 40 patients). The clinical efficacy (defined as the absence of symptoms) was 90.9% (40 of 44 patients) in the 3-day cefditoren group. Recurrence rate at 4 to 6 weeks after treatment completion was 10.2% (5 of 49 patients). *Escherichia coli* caused the majority of the infections in the 3-day group (84.3%).

The totality of evidence for 3-day regimens of oral β-lactams indicates significant variation in clinical and microbiological outcomes. As was seen with single dose β-lactam regimens, clinical failures or relapses often take place after the first week following treatment completion. It should be noted that outcomes with third generation cephalosporins appear to be numerically higher than those of earlier generation cephalosporins or penicillins, however the rationale for this observed difference is challenging to identify. Differences in half-lives as proposed by some of the study authors are often ameliorated by differences in dosing schemes. While wild type minimum inhibitory concentrations of Gram-negative organisms that commonly cause UTI (e.g., *Escherichia coli)* may be lower for third generation cephalosporins, urine concentrations of earlier generation cephalosporins can still exceed the pathogen MIC for an adequate amount of time to achieve established PK/PD targets. Higher prevalence of resistance to earlier generation cephalosporins and/or amoxicillin-containing β-lactams as compared to third generation cephalosporins could contribute to some of the difference that is seen, however some RCTs did not see a difference in outcomes when comparing susceptible and non-susceptible isolates perhaps because the drug levels achieved are so high in the urine for most β-lactams that they exceed the established breakpoints easily. Finally, it is possible that difference observed between various β-lactams may be simply due to chance.

5 days. We were only able to identify one RCT that investigated a 5-day duration of a β-lactam for the treatment of acute cystitis.[341]

Elhanan et al. published an RCT in Israel in 1994. The study population consisted of women 16 years of age or older (mean age = 37.2 years) with symptoms of cystitis who had a positive leukocyte esterase test who had not been treated with antibiotics in the last 4 weeks. Each enrolled patient had to demonstrate a microorganism sensitive to both of the antibiotics in the two treatment arms (fosfomycin and cephalexin). One of the treatment arms received 5-day treatment with cephalexin, a first generation cephalosporin, dosed at 500 mg four times daily. Each patient was monitored clinically and bacteriologically at day 5 and 28. At the follow-up visit on day 5, clinical cure (not precisely defined in the study) was achieved in 49 of 54 (91%) women in the cephalexin group. At the 28-day follow-up visit, 42 of 54 (78%) women continued to be asymptomatic. Bacteriologic cure (defined as "complete eradication" of all bacteria) was observed in 45 of 54 (83%) women at the 5-day follow-up visit and in 37 of 54 (68%) women at the 28-day follow-up visit. The majority of the initial infections (78%) and relapses/reinfections (63%) in the cephalexin group were due to *Escherichia coli*.

7 days. We found multiple RCTs that investigated a 7-day duration of a β-lactam for the treatment of cystitis (see table 11), many of which compared directly against shorter durations of the same β-lactam (see table 12).

Table 11. Clinical and microbiological outcomes of RCTs evaluating 7-day regimens of various β lactams for cystitis.

RCT (in chronologic order)	β-lactam	Dosing regimen (all for 7 days)	Clinical cure (specified time point)	Microbiologic cure (specified time point)
Sandberg et al.[360](1985)	Cefadroxil	1 gram once daily	86% (7 days) 72% (5 weeks)	
	Amoxicillin	375 mg three times daily	92% (7 days) 84% (5 weeks)	
Greenberg et al.[356](1986)	Cefadroxil	500 mg twice daily	83% (within 3 days) 70% (4 weeks)	
Hamasuna et al.[364](2014)	Faropenem	200 mg three times daily	80.2% (5 to 9 days) 50% (4 to 6 weeks)	66.7% (5 to 9 days) 38.6% (4 to 6 weeks)
Sadahira et al.[365](2017)	Cefditoren pivoxil	100 mg three times daily	93.2% (5 to 9 days)	90.2% (7 to 14 days)

Table 12. Clinical and microbiological outcomes of RCTs directly comparing multiple β-lactam durations for cystitis.

RCT (in chronological order) ***Treatment agent***	**Arm 1**	**Arm 2**	**Arm 3** (n/a = not applicable)	**Clinical cure comparison**	**Microbiologic cure comparison**
Sandberg et al.[360](1985) *Cefadroxil or amoxicillin*	3 days cefadroxil (1 g once daily)	7 days cefadroxil (1 g once daily)	7 days amoxicillin (375 mg TID)	At 1 week: 80% vs. 86% vs. 92% ($p > 0.1$) At 5 weeks: 75% vs. 72% vs. 84% ($p > 0.1$)	
Greenberg et al.[356](1986) *Cefadroxil*	Single dose (1 g)	3 days (500 mg BID)	7 days (500 mg BID)	Within 3 days: 47% vs. 68% vs. 83% At 4 weeks: 25% vs. 58% vs. 70%	
Raz et al.[358](1991) *Amoxicillin/clavulanate*	Single dose (1,500 mg/375 mg)	3 days (250 mg TID)	n/a	At 7 days: 78.1% vs. 87%, p = 0.33 At 4 weeks: 67.2% vs. 77.7%, p = 0.31	At 7 days: 70.9% vs. 83.3%, p = 0.18 At 4 weeks: 65.5% vs. 75.9%, p = 0.32
Sadahira et al.[365](2017) *Cefditoren pivoxil*	3 days (100 mg TID)	7 days (100 mg TID)	n/a	At 5 to 9 days post-treatment: 90.9% vs. 93.2%, p = 1.000	At 5 to 9 days post-treatment: 82.5% vs. 90.2%, p = 0.349

A notable retrospective cohort study published in 2022[366] compared 3 days of intravenous ceftriaxone to longer treatment (5 or more days) and found that there was no difference in clinical cure rates (100% in both groups) and less adverse events in the 3-day group, including new CDI infection or drug-related adverse effects. This data may suggest that 3 days of IV β-lactams overall is sufficient to treat cystitis, though this needs to be further investigated in randomized studies. This may also stimulate interest in the investigation of 3-day dose-optimized oral β-lactam treatment regimens for cystitis. The dosing of oral β-lactams included in prior studies have been generally low (e.g., 100 mg cefpodoxime proxetil twice daily, amoxicillin/clavulanate 500/125 mg twice daily, cefdinir 100 mg twice daily, etc.), so most authors believe equipoise exists regarding whether or not higher dosing may lead to different outcomes as it does in other scenarios, such as Gram-negative bacteremia (see the Gram-negative bacteremia from a urinary source section of this manuscript).

The totality of evidence makes it clear that the precise duration of treatment of cystitis in adults when using β-lactams remains uncertain and may vary by the specific β-lactam and dose used. Due to heterogeneity of the studies and included populations, we are unable to make a clear recommendation for a single duration of treatment. The 2020 network meta-analysis by Kim et al.[325] did not demonstrate a statistically significant difference between the effects of 3-day or 7-day third generation cephalosporin regimens with single dose third generation cephalosporin

regimens when it came to clinical response (3-day vs. single dose: RR = 1.04 [95% CrI: 0.85 to 1.34] and 7-day vs. single dose: RR = 1.02 [95% CrI: 0.75 to 1.39]), though the quality of evidence is rated very low and there was only 1 RCT to compare different durations of third generation cephalosporins (Sadahira et al, 2017).

Pivmecillinam

Pivmecillinam (PVM) was only recently approved by the United States Food and Drug Administration in April 2024, but has been used internationally for more than 40 years for lower urinary tract infections based on its specificity for the urinary tract, low perceived risk for collateral damage, and reasonable treatment efficacy based on prior RCTs (reviewed below). It does appear in the 2010 IDSA/ESCMID guideline as a treatment option in countries where it is available (strong recommendation, high quality of evidence).[104]

Nicolle published a systematic review in 2000 that reviewed results of various studies that evaluated pivmecillinam in the 1970s and 1980s.[367] Dosing regimens and durations were heterogenous in both comparative and non-comparative studies. In all studies included in the review, observed bacteriological cure rates (with varying definitions) were observed in 83-95% of patients with 3-day regimens, 85 to 100% of patients with 5-day regimens, 85 to 100% of patients with 7-day regimens and 79-90% of patients with 10-day regimens of pivmecillinam. Clinical outcomes were not addressed in this descriptive review.

Three RCTs have compared a 3-day duration of pivmecillinam with either placebo or other antimicrobials.[368–370] Outcomes from the pivmecillinam groups in those two studies are summarized briefly below. Evaluable RCTs comparing different durations of pivmecillinam are reviewed in table 13 below.

First, the RCT published by Menday in 2000[370] was conducted in 28 different “health institutions” in the United States and enrolled 440 adult outpatients with symptoms of cystitis with no more than two symptomatic episodes in the last year. Other exclusions included: pregnancy, hypersensitivity to study drugs, history of obstructive uropathy, and/or history of catheterization or instrumentation of the GU tract. Patients were randomized to receive either pivmecillinam 200 mg three times daily for 3 days or cephalexin 250 mg four times daily for 7 days. Clinical cure (elimination of initial symptoms at all three follow-up visits) or improvement (significant reduction in abnormal clinical findings, but incomplete resolution at last follow-up visit) was obtained in 95.3% of patients and bacteriological cure (urine culture with less than 10^5 CFU/mL of the initial pathogen at all three follow-up visits) occurred in 89.7% who received pivmecillinam. Both of these outcomes were similar to the comparator group with cephalexin. OR for clinical efficacy of PVM vs. cephalexin = 1.4 (95% CI: 0.4 to 4.6). OR for bacteriological efficacy of PVM vs. cephalexin = 1.96 (95% CI: 0.9 to 4.3). Combined, these suggest reliably efficacy of the 3-day duration of pivmecillinam and comparable efficacy to a comparator that is commonly used in contemporary practice.

Second, the RCT published by Nicolle et al. in 2002[368] was an international multi-center in which patients were enrolled in Austria, Belgium, Canada, Denmark, France, Ireland, The Netherlands, Switzerland, and the United Kingdom. The study population included non-pregnant

women between 18 and 65 years old who had symptoms of acute cystitis for 7 days or less. Subjects were excluded for a number of reasons including catheters, other GU tract abnormalities, recent treatment for UTI, recurrent UTI defined by 3 or more episodes in the last year, any antibiotics within the last 2 weeks, immunosuppression, diabetes, among others. Patients were contacted on study day 4 (+/- 1 day) and assessed symptoms and any adverse effects via telephone and returned for assessment on day 11 (+/- 2 days) and 39 (+/- 5 days). The primary outcome was the proportion of patients with a positive urine culture at enrollment who were bacteriologically cured at the early post-therapy visit (day 11). Bacteriologic cure was found in 222 of 298 (75%) of patients who received pivmecillinam at the day 11 (+/- 2 days) follow-up visit. At the day 39 (+/- 5 days) visit, 183 of 222 (82%) were found to have bacteriological cure. At the time of the telephone clinical assessment on day 4 (+/- 1 day), 434 of 457 (95%) patients who received pivmecillinam reported clinical cure (e.g., resolution of symptoms) OR improvement in symptoms. When assessed for clinical cure only at the day 11 and 39 visits, reported cure rates were 360 of 437 (82%) and 297 of 327 (91%), respectively.

Third, the RCT published by Vik et al. in 2018[369] consisted of a study population of non-pregnant women aged 18 to 60 years with symptoms of cystitis for less than 7 days. There were several exclusion criteria including signs of pyelonephritis, vaginal symptoms, severe abdominal pain, CKD, certain auto-immune conditions, use of certain medications (e.g., probenecid, steroids, anticoagulants), catheter use, among others. These patients were recruited from the accident and emergency outpatient clinics in Oslo and Bergen, Norway. Receiving pivmecillinam dosed at 400 mg twice daily for 3 days resulted in the proportion of patients who received pivmecillinam "feeling cured" by day 4 (the primary outcome measure) being 74%, rising to 91% and 94% by days 7 and 14, respectively. The median symptom duration after randomization was 3 days in the pivmecllinam group. After 14 days, only 10% of evaluable patients had positive urine cultures.

Table 13. Clinical and microbiological outcomes of RCTs directly comparing multiple pivmecillinam durations for cystitis.

RCT directly comparing multiple PVM durations (in chronological order)	**Arm 1**	**Arm 2**	**Arm 3** (n/a = not applicable)	**Clinical cure comparison**	**Microbiologic cure comparison**
Marsh and Menday[371](1980)	3 days (200 mg TID)	7 days (200 mg TID)	n/a	Symptomatic recurrences: 10.3% (3d) vs. 16.4% (7d) (2 to 3 days)	91% (3d) vs. 100% (7d) (2 to 3 days)
Sutlieff et al.[372](1982)	3 days (400 mg once, then	5 days (400 mg BID)	n/a	63% "entirely symptom free" (entire cohort, "a few	95% (3d) vs. 96% (5d) ("a few days after treatment")

	200 mg TID)			days after treatment")	
Richards et al.[345](1984)	3 days (400 mg BID)	7 days (400 mg BID)	n/a	67% vs. 62% (1 week)	95% vs. 100% (1 week)
Hovelius et al.[373](1985)	3 days (400 mg TID)	7 days (200 mg TID)	n/a	Gram-negative rods: 82.3% (3d) vs. 84% (7d) (4 weeks)	n/a
Pitkajarvi et al.[346](1990)	3 days (400 mg TID)	7 days (200 mg TID)	n/a	n/a	91% vs. 94% (1st control) 88% vs. 95% (2nd control)
Ferry et al.[347](2007)	3 days (400 mg BID)	7 days (200 mg BID)	7 days (400 mg TID)	Days 8 to 10: 55% vs. 62% vs. 64%, p = 0.16 Days 35 to 49: 68% vs. 72% vs. 65%, p = 0.37	Days 8 to 10: 84% vs. 94% vs. 93%, p < 0.001 Days 35 to 49: 86% vs. 89% vs. 83%, p = 0.21
Jansaker et al.[374](2019)	5 days (400 mg TID)	3 days (400 mg TID)	n/a	Mean number of days to symptom resolution: 2.91 days vs. 2.94 days (RD = -0.03 days [95% CI: -0.4 to 0.3]) End of intervention: 73% vs. 76% (RD = 3.2% [95% CI: -7.1 to 13.5])	At 7 to 21 days: 88% vs. 87% (RD = 1.6% [95% CI: -8.4 to 11.6]) At 15 to 42 days: 91% vs. 84% (RD = 6.8% [95% CI: -3.9 to 17.5])

Richards published a multi-center study in the general practice setting in 1984 in England, enrolling non-pregnant women aged 18 to 55 years old with symptoms of urinary frequency and dysuria.[345] Patients with renal or hepatic disease, anatomical GU issues, or UTI during the previous month were excluded. The severity of the enrolled patients' symptoms was scored on an ordinal scale with a maximum number of points of 15. Mean pre-treatment symptom scores were 7.22 and 7.42 for the 3-day and 7-day groups, respectively. Both scores were reduced to a mean

score of 0.87 in both groups following treatment. Eight patients experienced recurrences in the 4-week follow-up period (6 in the 3-day group and 2 in the 7-day group). Significant bacteriuria was defined as 10^5 or more CFU/mL of urine. Bacteriological success (absence of significant bacteriuria) rates were 95% for the 3-day regimen and 100% for the 7-day regimen. Overall *in vitro* susceptibility to mecillinam among 55 available (mostly *E. coli*) isolates was 84%.

Ferry et al. (2007)[347] published a randomized, double-blind, multi-center, placebo-controlled trial at 18 primary healthcare centers in northern Sweden. Women aged 18 years or older with symptoms of cystitis were eligible to participate. Women who were on antibiotics for UTI in the last month, had complicating factors (e.g., GU tract abnormalities or diabetes), or signs of pyelonephritis were excluded. Patients with significant bacteriuria (defined as ≥ 10^5 CFU/mL) were followed up at two visits (after 8 to 10 days and after 35 to 49 days). Clinical cure was defined as no persisting symptoms post-treatment. Bacteriological cure was defined as eradication of initial bacteriuria at the follow-up visits. *Escherichia coli* was the predominating uropathogen. Group A (n = 217) received 200 mg three times daily for 7 days.5 Group B (n = 220) received 200 mg twice daily for 7 days. Group C (n = 220) received 400 mg twice daily for 3 days. Results are reflected above in table 13. Generally, the authors found that 7-day regimens were more effective than 3-day regimens in terms of clinical and bacteriological cure, although only comparison with a statistically significant difference was in bacteriological cure at days 8 to 10 ($p < 0.001$).

Jansaker et al. (2019)[374] published a multi-center, placebo-controlled, double-blinded randomized trial at 9 general practice clinics in Denmark. The study population included women 18 to 70 years old presenting with symptoms of dysuria, frequency, and/or urgency. Patients on antibiotic therapy at time of presentation, with vaginal discharge, recurrent UTI in the last month, pregnancy, or signs or symptoms of pyelonephritis were excluded. The primary clinical outcome was mean number of days to symptom resolution and proportion of patients cured at last day of treatment. Bacteriological success was defined as either no growth or a significant reduction (of over 10^2 CFU/mL) in the first control urine sample. One group received 5 days of pivmecillinam while the other group received 3 days. The mean number of days to symptom resolution in the 5-day group was 2.91 days compared with 2.94 days in the 3-day group (RD = -0.03 days [95% CI: -0.4 to 0.3 days). Clinical success at the end of the intervention was observed in 117 of 153 (76%) in the 5-day group and 115 of 157 (73%) in the 3-day group (RD = 3.2% [95% CI: -7.1 to 13.5%]). Bacteriological success between days 7 and 21 was seen in 92 of 104 (88%) of the 5-day group patients and in 86 of 99 (87%) of the 3-day group patients (RD = 1.6% [95% CI: -8.4 to 11.6%]). Between days 15 and 42, there was a larger difference in bacteriological success (82 of 90 [91%] patients in the 5-day group compared with 75 of 89 [84%] in the 3-day group for a risk difference of 6.8% [95% CI: -3.9 to 17.5%]).

Three studies that appear to be un-published were conducted and ultimately led to FDA approval of the new pivmecillinam formulation in the United States in 2024. These trials are summarized in the package insert[344] and in table 14 below:

Table 14. Clinical and microbiological outcomes of RCTs included in the Pivya (pivmecillinam) package insert.

RCT *Clinicaltrials.gov study # (if available)*	Number of subjects that received PVM	PVM dosing & duration	Clinical cure (specified time point)	Microbiologic cure (specified time point)
"Trial 1"	137	185 mg* TID for 7 days; 185 mg BID for 7 days; 370 mg BID for 3 days	85 of 137 patients (62%); results not available stratified by dosing regimen; Statistically better outcomes in composite response rate vs. placebo comparator; RD = 52% (95% CI: 41 to 62%)	
"Trial 2"	127	185 mg* TID for 3 days	91 of 127 (72%) No statistical difference in composite response rate vs. cephalexin comparator (250 mg QID for 7 days); RD = -4% (95% CI: -16 to 7%)	
"Trial 4" *NCT 01849926*	105	185 mg* TID for 3 days	69 of 105 patients (66%); Statistically better outcomes in composite response rate vs. ibuprofen comparator; RD = 44% (95% CI: 31 to 57%)	

*Note 185 mg pivmecillinam is equivalent to 200 mg pivmecillinam hydrochloride

When evaluating the totality of the evidence for pivmecillinam, there was significant variability in dosing regimens and durations used in available trials. A meta-analysis of 24 RCTs published by Pinart et al (2017) demonstrated that there does not appear to be a negative effect on efficacy when using short duration regimens of pivmecillinam, such as three days.[375] Additionally, the 2020 network meta-analysis by Kim et al. did not find a statistically significant difference between the 5-day and 3-day pivmecillinam regimens (clinical response: RR = 1.04 [95% CrI: 0.91 to 1.19] and microbiological response: RR = 1.02 [95% CrI: 0.9 to 1.15]). There was also not statistical difference found when comparing the 7-day and 3-day pivmecillinam regimens (clinical response: RR = 1.1 [95% CrI: 0.999 to 1.2] and microbiological response: RR = 1.06 [95% CrI: 0.99 to 1.15]).[325]

Trimethoprim/sulfamethoxazole

Several randomized controlled trials have evaluated a 3-day course of trimethoprim/sulfamethoxazole (TMP/SMX) for the treatment of uncomplicated cystitis and found 3 days to be as effective as longer courses of TMP/SMX either in comparison to longer durations of TMP/SMX or (more commonly) in comparison with other commonly used antimicrobials for urinary tract infections, such as fluoroquinolones which have been compared against longer durations of TMP/SMX.[376] As such, many more recent studies have used a 3-day course of TMP/SMX as a comparator when testing efficacy of shorter durations of other agents for cystitis.[328,336,350,356,363,377,378]

We found 2 RCTs that directly compared 3-day durations to durations shorter than 3 days for TMP/SMX. Gossius and Vorland (1984)[328] compared single dose (320 mg TMP) with 3-day

(160 mg TMP twice daily and 10-day treatment regimens in 464 female outpatients with symptoms suggestive of acute cystitis and found similar rates of "poor clinical response" in all three groups (7.5% [7 of 93] in the single dose group, 9.9% [9 of 91] in the 3-day group, and 6.3% [6 of 95] in the 10-day group). Additionally, bacteriologic response including number of relapses, reinfections, and those free of bacteriuria were similar across all three groups at follow-up at 2- and 6-weeks post treatment. A multi-arm RCT[356] included (among others) an arm for single dose (320 mg TMP) and 3-day courses (160 mg TMP twice daily) of TMP/SMX and found higher microbiologic cure rates with 3-day course (88%) compared with the single dose (65%) course (p = 0.13), however the authors noted that all bacteriologic failures were also symptomatic (clinical failures).

An RCT by Trienekens et al (1989) compared 3 days to 7 days of TMP/SMX in females aged 12 to 65 years old presenting to their general practitioner with symptoms suggestive of cystitis.[376] Patients were excluded if they had signs or symptoms of acute pyelonephritis, diabetes, structural abnormalities of the GU tract, indwelling catheters, recently received immunosuppressive drugs, or had received antimicrobial treatment within the last 4 weeks. In both arms, patients received equivalent to one double-strength tablet (800 mg sulfamethoxazole and 160 mg trimethoprim) twice daily. At one week post study entry, symptoms were absent or improved in 131 of 142 (92%) of patients in the 3-day group and 129 of 145 (89%) patients in the 7-day group. After 2 weeks, symptoms were absent or improved in 110 of 121 (91%) patients in the 3-day group and 108 of 121 (89%) patients in the 7-day group. Long-term follow-up at 6 weeks saw symptoms absent in 97 of 116 (84%) patients in the 3-day group and 106 of 123 (86%) in the 7-day group.

A 2020 network meta-analysis of these RCTs using Bayesian hierarchical random-effects model for dichotomous outcomes found the 3-day regimen more effective than a single dose regimen of TMP/SMX in terms of clinical response (RR = 1.15 [95% CrI: 1.01 to 1.31]), but not microbiologic response (RR = 1.02 [95% CrI: 0.95 to 1.1]).[325] As such, while it appears likely that a single dose of TMP/SMX may be more effective than placebo, there is not enough high-quality evidence to suggest that a single dose of TMP/SMX is as effective as a 3-day course. Given the totality of the evidence available, we are able to make a clear recommendation for 3-days of treatment with TMP/SMX for acute cystitis in adults.

Fluoroquinolones

Numerous RCTs have compared various durations of treatment with fluoroquinolones (FQs) ranging from single dose to 7 days. Table 15 below reviews pertinent RCTs which directly compare different durations of fluoroquinolones within the same generation to inform practice on optimal duration of treatment for cystitis.

Table 15. Clinical and microbiological outcomes of RCTs directly comparing multiple fluoroquinolone durations for cystitis within the same fluoroquinolone generation.

RCT directly comparing multiple durations within the same FQ generation (in chronological order) ***Generation of FQ***	**FQ Arm 1 (dosing)**	**FQ Arm 2 (dosing)**	**FQ Arm 3 (dosing)** n/a = not applicable	**Clinical cure comparison**	**Microbiologic cure comparison**
Inter-Nordic UTI Study Group [379](1988) *2nd generation*	Norfloxacin (400 mg BID for 3 days)	Norfloxacin (400 mg BID for 7 days)	n/a	Median time to disappearance of symptoms: 3 days (3d) vs. 3 days (7d)	3 to 13 days: 93.8% (3d) vs. 96.6% (7d) 45 days: 81.3% (3d) vs. 91.7% (7d)
Hooton et al.[329](1989) *2nd generation*	Ofloxacin (200 mg BID for 3 days)	Ofloxacin (200 mg BID for 7 days)	Ofloxacin (300 mg BID for 7 days)	n/a	1 week: 96% (3d) vs. 91% (200mg 7d) vs. 96% (300mg 7d) 4 weeks: 88% (3d) vs. 86% (200mg 7d) vs. 100% (300mg 7d)
Van Balen et al.[380](1990) *2nd generation*	Pefloxacin (800 mg single dose)	Norfloxacin (400 mg BID for 5 days)	n/a	8 to 10 days: 76% (PEFX) vs. 78% (NFLX) 6 weeks: 80% (PEFX) vs. 81% (NFLX)	8 to 10 days: 88% (PEFX) vs. 87% (NFLX) 6 weeks: 79% (PEFX) vs. 72% (NFLX)
Hooton et al.[381](1991) *2nd generation*	Ofloxacin (400 mg single dose)	Ofloxacin (200 mg BID for 3 days)	n/a	n/a	5 to 9 days: 93% (single dose) vs. 92% (3d) 4 to 6 weeks: 81% (single dose) vs. 89% (3d)

Saginur and Nicolle[382] (1992) *2nd generation*	Norfloxacin (800 mg single dose)	Norfloxacin (400 mg BID for 3 days)	n/a	n/a	3 days: 88% (single dose) vs. 98% (3d) 7 days: 81% (single dose) vs. 94% (3d) 4 to 6 weeks: 78% (single dose) vs. 88% (3d)
Neringer et al.[330](1992) *2nd generation*	Lomefloxacin (400 mg daily for 3 days)	Lomefloxacin (400 mg daily for 7 days)	Norfloxacin (400 mg BID for 7 days)	5 to 9 days: 84% (LMFX 3d) vs. 87% (LMFX 7d) vs. 85% (NFLX) 3 to 4 weeks: 72% (LMFX 3d) vs. 73% (LMFX 7d) vs. 73% (NFLX)	5 to 9 days: 88% (LMFX 3d) vs. 93% (LMFX 7d) vs. 93% (NFLX) 3 to 4 weeks: 81% (LMFX 3d) vs. 82% (LMFX 7d) vs. 85% (NFLX)
Trienekens et al.[331](1993) *2nd generation*	Norfloxacin (400 mg BID for 3 days)	Norfloxacin (400 mg BID for 7 days)	n/a	1 week after initiation: 95% (3d) vs. 90% (7d), *p = 0.13* 6 weeks after initiation: 93% (3d) vs. 93% (7d), *p = 0.8*	1 week after initiation: 92% (3d) vs. 95% (7d), *p = 0.3* 6 weeks after initiation: 82% (3d) vs. 88% (7d), *p = 0.3*
Iravani et al.[383](1993) *2nd generation*	Fleroxacin (200 mg single dose)	Fleroxacin (400 mg single dose)	Ciprofloxacin (250 mg BID for 7 days)	5 to 9 days: 93.6% (FLXN single) vs. 97.2% (FLXN 7d) vs. 98% (CIP), *p = NS*	5 to 9 days: 88% (FLXN single) vs. 96% (FLXN 7d) vs. 96% (CIP), $p < 0.05$ 4 to 6 weeks: 91% (FLXN single) vs. 89% (FLXN 7d) vs. 93% (CIP), *p = NS*

Del Río et al.[384](1996) *2nd generation*	Rufloxacin (400 mg single dose)	Norfloxacin (400 mg BID for 5 days)	n/a	8 to 12 days: 93.9% (RFLX) vs. 96% (NFLX) 4 to 6 weeks: 92% (RFLX) vs. 93% (NFLX)	8 to 12 days: 93.9% (RFLX) vs. 98.6% (NFLX) 4 to 6 weeks: 95.3% (RFLX) vs. 96.3% (NFLX)
Goto et al.[362](1999) *2nd generation*	Ciprofloxacin (200 mg single dose)	Ciprofloxacin (200 mg daily for 3 days)	Ciprofloxacin (200 mg BID for 3 days)	End of treatment or 3d post single dose: 64% (CIP single) vs. 77.8% (CIP daily 3d) vs. 63% (CIP bid 3d)	End of treatment or 3d post single dose: 88% (CIP single) vs. 85.2% (CIP daily 3d) vs. 85.2% (CIP bid 3d)
Auquer et al.[385](2002) *2nd generation*	Ciprofloxacin (500 mg single dose)	Norfloxacin (400 mg BID for 3 days)	n/a	7 days: 91.2% (CIP) vs. 93.8% (NFLX)	7 days: 91.2% (CIP) vs. 91.9% (NFLX)
Richard et al.[386](2002) *4th generation*	Gatifloxacin (400 mg single dose)	Gatifloxacin (200 mg daily for 3 days)	n/a	5 to 9 days: 93% (GAT single) vs. 95% (GAT 3d) 29 to 42 days: 90% (GAT single) vs. 88% (GAT 3d)	5 to 9 days: 92% (GAT single) vs. 96% (GAT 3d)
Arredondo-Garcia et al.[332](2004) *2nd generation*	Ciprofloxacin (250 mg BID for 3 days)	Norfloxacin (400 mg BID for 7 days)	n/a	Overall composite success: 5 to 9 days: 83.5% (CIP) vs. 78.5% (NFLX) 4 to 6 weeks: 77.3% (CIP) vs. 80.4% (NFLX)	
				5 to 9 days: 88.7% (CIP) vs. 84.1% (NFLX) 4 to 6 weeks:	5 to 9 days: 91.8% (CIP) vs. 86.9% (NFLX) 4 to 6 weeks:

				83.5% (CIP) vs. 82.2% (NFLX)	83.5% (CIP) vs. 81.3% (NFLX)
Vogel et al.[333](2004) *2nd generation*	Ciprofloxacin (250 mg BID for 3 days)	Ciprofloxacin (250 mg BID for 7 days)	n/a	n/a	2 days after treatment completion: 93% (7d) vs. 98% (3d), *RD = -5% (95% CI: -11.9 to 1.9%)*
Naber et al.[387](2004) *4th generation*	Gatifloxacin (400 mg single dose)	Gatifloxacin (200 mg daily for 3 days)	n/a	7 to 9 days: 81.1% (GAT single) vs. 85.2% (GAT 3d) 4 to 6 weeks: 81.6% (GAT single) vs. 88% (GAT 3d)	7 to 9 days: 80.5% (GAT single) vs. 82.9% (GAT 3d) 4 to 6 weeks: 74.6% (GAT single) vs. 79.3% (GAT 3d)
Haghighi et al.[334](2010) *2nd generation*	Ciprofloxacin (250 mg BID for 3 days)	Ciprofloxacin (250 mg BID for 7 days)	n/a	4 weeks: 74.4% (3d) vs. 70.3% (7d)	End of treatment: 66.7% (3d) vs. 64.8% (7d)

Table 16 below illustrates comparisons between generations of fluoroquinolones and the concept that higher generations of fluoroquinolones (e.g., 3rd or 4th generation fluoroquinolones) may result in better clinical and/or microbiological outcomes when given for the same duration and/or that shorter durations of higher generation fluoroquinolones may be similarly effective to longer durations of earlier generation fluoroquinolones.

Table 16. Clinical and microbiological outcomes of RCTs directly comparing multiple fluoroquinolone durations for cystitis across different fluoroquinolone generations.

RCT directly comparing durations using FQ from different generations (in chronological order)	**FQ Arm 1 *FQ gen.* (dosing)**	**FQ Arm 2 *FQ gen.* (dosing)**	**FQ Arm 3 *FQ gen.* (dosing)** n/a = not applicable	**Clinical cure comparison**	**Microbiologic cure comparison**
Stein and Philip[388](1992)	Ciprofloxacin *2nd gen.* (250 mg BID for 7 days)	Temafloxacin *3rd gen.* (400 mg daily for 3 days)	n/a	5 to 9 days: 95% (CIP) vs. 90% (TEMA)	5 to 9 days: 96% (CIP) vs. 97% (TEMA)
Henry et al.[389](1998)	Ofloxacin *2nd gen.* (200 mg BID for 3 days)	Sparfloxacin *3rd gen.* (400 mg on day 1, then 200 mg daily for 2 days)	n/a	5 to 9 days: 94.7% (OFLX) vs. 92.3% (SPAR)	5 to 9 days: 97.1% (OFLX) vs. 95.7% (SPAR)
Henry et al.[390](1999)	Ciprofloxacin *2nd gen.* (250 mg BID for 7 days)	Sparfloxacin *3rd gen.* (400 mg single dose)	Sparfloxacin *3rd gen.* (400 mg on day 1, then 200 mg daily for 2 days)	5 to 9 days: 91.6% (CIP) vs. 91.8% (SPAR single) vs. 92.2% (SPAR 3d) 4 to 6 weeks: 79.5% (CIP) vs. 76.6% (SPAR single) vs. 80.2% (SPAR 3d)	5 to 9 days: 96.6% (CIP) vs. 91.7% (SPAR single) vs. 92.6% (SPAR 3d) 4 to 6 weeks: 92.6% (CIP) vs. 80.7% (SPAR single) vs. 90.1% (SPAR 3d)
Richard et al.[391](2000)	Ofloxacin *2nd gen.* (200 mg BID for 3 days)	Levofloxacin *3rd gen.* (250 mg daily for 3 days)	n/a	5 to 9 days, per-protocol: 97% (OFLX) vs. 98.1% (LVX)	5 to 9 days: 93.6% (OFLX) vs. 96.3% (LVX)

				5 to 9 days, ITT: 94.3% (OFLX) vs. 96.3% (LVX)	
Richard et al.[386](2002)	Gatifloxacin *4th gen.* (400 mg single dose)	Gatifloxacin *4th gen.* (200 mg daily for 3 days)	Ciprofloxacin *2nd gen.* (100 mg BID for 3 days)	5 to 9 days: 93% (GAT single) vs. 95% (GAT 3d) vs. 93% (CIP) 29 to 42 days: 90% (GAT single) vs. 88% (GAT 3d) vs. 92% (CIP)	5 to 9 days: 92% (GAT single) vs. 96% (GAT 3d) vs. 94% (CIP)
Cervigni et al.[392](2004)	Pefloxacin *2nd gen.* (800 mg single dose)	Prulifloxacin *4th gen.* (600 mg single dose)	n/a	5 to 7 days: 84.3% (PEFX) vs. 92.2% (PRU) 4 weeks: 96.5% (PEFX) vs. 97.4% (PRU)	5 to 7 days: 92.2% (PEFX) vs. 97.4% (PRU) 4 weeks: 97.4% (PEFX) vs. 99.1% (PRU)
Naber et al.[387](2004)	Ciprofloxacin *2nd gen.* (250 mg BID for 3 days)	Gatifloxacin *4th gen.* (400 mg single dose)	Gatifloxacin *4th gen.* (200 mg daily for 3 days)	7 to 9 days: 81.1% (GAT single) vs. 85.2% (GAT 3d) vs. 84.5% (CIP) 4 to 6 weeks: 81.6% (GAT single) vs. 88% (GAT 3d) vs. 85.8% (CIP)	7 to 9 days: 80.5% (GAT single) vs. 82.9% (GAT 3d) vs. 81.5% (CIP) 4 to 6 weeks: 74.6% (GAT single) vs. 79.3% (GAT 3d) vs. 78.8% (CIP)

Based on moderate quality evidence, the 2020 network meta-analysis by Kim et al.[325] found that a 3-day regimen of a 2nd generation fluroquinolone was statistically significantly more effective than a single dose of the same drug (clinical response: RR = 1.04 [95% CrI: 1.01 to 1.08] and microbiological response: RR = 1.04 [95% CrI: 1.003 to 1.08]). There was not a statistically significant difference found when comparing a 3-day regimen of a 3rd generation fluoroquinolone with a single dose of the same drug (clinical response: RR = 0.99 [95% CrI: 0.94 to 1.05] and microbiological response: RR = 1.03 [95% CrI: 0.96 to 1.11]). Similarly, there not a statistically significant difference found when comparing a 3-day regimen of a 4th generation fluoroquinolone with a single dose of the same drug (clinical response: RR = 1.02 [95% CrI: 0.97 to 1.08] and microbiological response: RR = 1.03 [95% CrI: 0.97 to 1.09]). Of note, the only 4th generation fluoroquinolone available in the United States is moxifloxacin, which due to its metabolism and elimination, should not routinely be used for the treatment of urinary tract infections; it has no FDA indication for urinary infections and achieves likely suboptimal levels in the urine.[393] The totality of the evidence on fluoroquinolone use clearly demonstrates their reliable efficacy in the treatment of urinary tract infections using a variety of members of the class for various durations, however this should be viewed in the context of increasing resistance rates amongst common uropathogens at the individual and ecological levels[394,395] and the potential for collateral damage from potentially catastrophic side effects of the drugs.[396–398]

Fosfomycin

There are no prospective RCTs evaluating different dosing durations of oral fosfomycin. Only single dose regimens have been studied to date. A summary of the available RCTs are shown below in table 17.

Table 17. Clinical and microbiological outcomes of patients receiving single dose fosfomycin for cystitis in published RCTs.

RCT (in chronologic order)	Number of subjects that received fosfomycin in analysis*	% *E. coli* pathogens in fosfomycin group	Clinical cure (specified time point)	Microbiologic cure (specified time point)
Boerema and Willems[335](1990)	61	75.4%	92% (1 to 2 days after 7-day double blind period) 65% (6 weeks)	90% (2 to 3 days) 62% (6 weeks)
Crocchiolo et al.[336](1990)	19	80%	92.1% cured OR improved (5 days)	100% (5 days) 89.4% (4 weeks)
Selvaggi et al.[337](1990)	28	89.2%	80% (7 days)	75% (7 days)

Naber and Thyroff-Friesinger[338](1990)	194	CFU ≥ 10^5: 88% CFU 10^2-10^4: 75% (includes mixed infections)	CFU ≥ 10^5, cured OR improved: 94.7% (1 week); 81.9% (4 weeks) CFU 10^2-10^4, cured OR improved: 95.2% (1 week); 87.5% (4 weeks)	CFU ≥ 10^5: 87.4% (1 week); 88.2% (4 weeks) CFU 10^2-10^4: 86.4% (1 week); 92.5% (4 weeks)
de Jong et al.[339](1991)	38	70.5%	n/a	93.9% (3 to 4 days) 73.3% (25-30 days)
Van Pienbroek et al.[351](1993)	116	n/a	94% cured OR improved (4 days) 95% cured OR improved (9 days) 82% cured OR improved (42 days)	81% (9 days) 93% (42 days)
Elhanan et al.[341](1994)	58	86.2%	91% (5 days) 86% (1 month)	91% (5 days) 81% (1 month)
Minassian et al.[342](1998)	204	77.8% (entire cohort)	n/a	83% (7 to 9 days)
Stein et al.[354](1999)	375	84%	82.1% (5 to 11 days after dose) 90.4% (5 to 11 days after 7-day double blind period) 91.1% (4 to 6 weeks)	78.1% (5 to 11 days after dose) 86.9% (5 to 11 days after 7-day double blind period) 96% (4 to 6 weeks)
Ceran et al.[343](2010)	77	79.2%	83.1% (7 days)	83.1% (7 days)
Huttner et al.[214](2018)	258	65%	66% (14 days) 58% (28 days)	73% (14 days) 63% (28 days)

*All subjects in all studies included received 3 grams of oral fosfomycin tromethamine as a single dose

Multiple retrospective cohort studies have been published since the 2010 IDSA/ESCMID guideline evaluating fosfomycin use for UTIs, specifically in the kidney transplant recipient

(KTR) population. Lopez-Medrano et al. (2020)[399] published a multicenter (total n = 14 hospitals, 143 episodes of cystitis) retrospective cohort study evaluating the chance for clinical cure at the end of therapy and microbiological cure at 1-month. A median dose of 1.5 grams fosfomycin was administered daily for a median of 7 days. Clinical cure (remission of symptoms by end of therapy) was achieved in 83.9% episodes. Among those with follow-up urine cultures at 1 month, microbiologic cure was 70.2%. Ten Doesschate et al. (2019)[400] also published a retrospective review of 53 episodes of cystitis in KTRs in which oral fosfomycin was used. Clinical cure rates were 67% for lower UTI and 80% for upper UTI (as "step-down" treatment after initial IV antibiotics). Both studies concluded that fosfomycin was a reasonable option for cystitis, however published clinical cure rates in these retrospective studies were notably less than what was reported based on the 2010 IDSA/ESCMID guideline[104] and other commonly used UTI therapeutic options.

It should be noted that injectable fosfomycin for intravenous use is available outside of the United States and our review found no RCTs that evaluated injectable fosfomycin in the treatment of cystitis without other systemic symptoms of infection. The ZEUS trial, evaluating the use of intravenous fosfomycin for the treatment of complicated UTI including pyelonephritis in comparison to piperacillin/tazobactam is discussed in the acute pyelonephritis section of this manuscript.[240]

Based on the totality of the evidence available, we are able to provide a clear recommendation for a single dose of fosfomycin for the treatment of cystitis. The authors acknowledge the possibility that a different dosing regimen may be more reliable (e.g., 2 or more doses), but there are no rigorous prospective studies to inform this practice.

Parenteral aminoglycosides

The data supporting the use of single-dose parenteral aminoglycosides is observational and hypothesis generating in nature. A comprehensive systematic review was published by Goodlet at al. in 2019.[230] A total of 13 studies were included in the qualitative analysis. Of note, only 4 of the 13 studies[293,294,401,402] included adult patients and very few studies evaluated clinical outcomes. As references at the beginning of this section, whether or not microbiological outcomes can be extrapolated to predict clinical outcomes (or visa versa) is not well understood. These studies are reviewed in table 18 below and are limited in scope by their observational nature and small number of subjects.

Table 18. Clinical and microbiological outcomes of adult patients receiving single dose parenteral aminoglycosides for cystitis in published RCTs.

Study including adults (in chronological order)	Total number of patients	Aminoglycoside and dose	Clinical cure	Microbiologic cure
Bailey et al.[401](1984)	22 (all adults)	Netilmicin 150 mg once	n/a	95%

Prát et al.[402](1984)	44 (all adults)	Netilmicin 300 mg once	n/a	89%
Rocca Rossetti et al.[293](1986)	13,258 (mixed, including adults)	Amikacin 500 mg once	83%	n/a
Caramalli et al.[294](1991)	76 (all adults)	Amikacin 15 mg/kg once or netilimicin 5 mg/kg once	95%	96%

A small prospective cohort study was published by Jenrette and colleagues in 2024 in which 13 patients were given a single of either 15 mg/kg amikacin (n = 8), 5 mg/kg gentamicin (n = 4), or 5 mg/kg tobramycin (n = 1).[[403]] Primary outcomes were clinical or microbiologic failure within 14 days of treatment. 11 of 13 patients (85%) reported no new urinary symptoms since discharge. No patients required hospitalization for treatment failure and no adverse events were noted. Although the prospective nature of this study is welcomed, obviously conclusions are limited based on the small sample size. Overall, we are unable to provide a clear recommendation for the use of single dose aminoglycosides.

Gepotidacin

Gepotidacin is a first-in-class triazaacenaphytyelene antibiotic that inhibits two type II bacterial topoisomerase enzymes, resulting in inhibition of bacterial DNA replication and bactericidal activity. EAGLE-2 and EAGLE-3 were randomized, multi-center, double-blind, double-dummy, non-inferiority (NI margin = 10%) trials in which non-pregnant, biologically female patients over 12 years old and weighing more than 40 kg received gepotidacin 1,500 mg twice daily for 5 days in one of the treatment arms.[[349]] The primary endpoint of "therapeutic response" at the test-of-cure visit (day 10 to 13) was defined as combined clinical success (complete symptom resolution) and microbiological success (reduction of qualifying uropathogens to less than 10^3 CFU/mL). In EAGLE-2, therapeutic success was achieved in 50.6% of 320 patients assigned to the 5-day course of gepotidacin. In EAGLE-3, therapeutic success was achieved in 58.5% of 277 patients assigned to the 5-day course of gepotidacin. No other durations of gepotidacin have been evaluated for the treatment of cystitis. Of note, both EAGLE-2 and EAGLE-3 were stopped after an interim analysis due to efficacy. Because of the early termination, only patients who had the opportunity to reach the test-of-cure visit or were known to not have attained therapeutic success were included.

Q22: What is the appropriate duration of treatment for acute pyelonephritis and/or febrile UTI in adults?

Executive summary

Based on several randomized trials, we can provide a clear recommendation on the duration of therapy for the following antimicrobial classes (regardless of biological sex) for the treatment of acute pyelonephritis:

- Fluoroquinolones: 5 to 7 days[119,120,239,309,404,405]
- Dose-optimized β lactams: 7 days[406–409]

We cannot provide clear recommendations for pyelonephritis treatment duration with trimethoprim/sulfamethoxazole, fosfomycin, or aminoglycoside monotherapy due to lack of reproducible high-quality data or heterogeneity across small studies.

We are unable to provide a clear recommendation for the treatment duration for febrile UTI. When considering the available data for pyelonephritis and Gram-negative bacteremia from a urinary source, it may be reasonable for febrile UTI to be treated in a similar fashion to pyelonephritis.

Overall summary

Trimethoprim/sulfamethoxazole

Historically, societal guidelines have recommended a treatment duration of 14 days for trimethoprim/sulfamethoxazole when treating pyelonephritis based on early RCTs that primarily utilized 14 day durations for TMP/SMX.[104] We were unable to identify any specific studies comparing different durations of TMP/SMX in the context of acute pyelonephritis, thus are unable to provide a clear recommendation for the duration of treatment when using TMP/SMX.

A small RCT by Bennett and Craven (1976)[410] featured 5 patients with "proved upper tract infection" (pyelonephritis) treated with TMP/SMX at a dose equivalent to one single-strength tablet (80 mg TMP) twice daily for 14 days. They report 100% bacteriological cure when checked 2 weeks after the completion of treatment.

A randomized trial by Stamm et al (1987)[411] included 21 women who received 2 weeks of TMP/SMX and 12 women who received 6 weeks of TMP/SMX. Cure rates (defined as eradication of the initially infecting strain and absence of recurrent infection symptoms in the 6-week follow-up period) using TMP/SMX were numerically higher in the 2 week group compared with the 6-week group, though not statistically significant (90% vs. 83%, respectively; 95% CI: -0.18 to 0.32).

Other small RCTs by Johnson et al (1991)[412] and Mouton et al (1992)[413] also utilized 14-day courses of TMP/SMX compared against ampicillin and lomefloxacin, respectively

In the RCT by Talan et al (2000)[239], clinical cure was only 83% in the TMP/SMX group despite 14 days of treatment and was inferior to 7 days of ciprofloxacin. This would generally suggest that a duration of 14 days is not long enough, however this difference in clinical cure appeared to be driven primarily by a higher resistance rate to TMP/SMX (18% to *Escherichia coli*, which caused over 90% of the infections in the study) than with ciprofloxacin (no isolates were resistant to ciprofloxacin). Subgroup analysis identified a cure rate of 92% in the patients with isolates susceptible to TMP/SMX compared with 35% in those resistant to TMP/SMX (95% CI: 0.29 to 0.83).

Drekonja et al (2021) published a randomized, double-blinded, placebo-controlled trial (NI margin = 10%) at two Veteran's Affairs hospitals investigating afebrile men treated for UTI in the outpatient setting and initially prescribed 7 to 14 days of ciprofloxacin (57.4%) or trimethoprim/sulfamethoxazole (42.6%).[122] In order to be eligible, these men had to have new onset symptoms including at least one of the following: dysuria, urinary frequency or urgency, hematuria, CVA tenderness, or perineal/flank/suprapubic pain. In the primary analysis of resolution of UTI symptoms 14 days after stopping active antimicrobials, treatment with 7 days of ciprofloxacin or trimethoprim/sulfamethoxazole was non-inferior to treatment for 14 days (93.1% in the 7-day group vs. 90.2% in the 14-day group; RD = 2.9% [one-sided 97.5% CI: -5.2% to ∞). In a post-hoc analysis, symptom resolution occurred in 147 of 156 (94.2%) patients who received ciprofloxacin compared with 101 of 116 (87.1%) patients who received trimethoprim/sulfamethoxazole ($p = 0.054$). The treatment duration by drug treatment interaction was not statistically significant (p = 0.37), indicating that any drug effect on resolution of symptoms did not significantly differ by treatment duration.

Additionally, there are three RCTs evaluating 7 versus 14 day durations for Gram-negative BSI[414–416], all of which featured a urine source of the BSI for the majority of included patients. Additional discussion of these studies are available in question 24. They may be relevant in the context of acute pyelonephritis as the most common portal of entry into the bloodstream from an ascending urinary tract infection is via the renal vasculature. As such, it is reasonable to assume that the majority of the urine source bloodstream infections included in the referenced RCTs are likely due to pyelonephritis.

Observational studies that provide some level of information on the duration of TMP/SMX for pyelonephritis are reviewed below:

Carrie et al (2004)[417] utilized an administrative healthcare claims database to determine effectiveness of TMP/SMX and fluoroquinolones for pyelonephritis in women (median age in the TMP/SMX group was 33 years). The authors used multivariate analyses to predict factors in treatment failure. The authors found that the interaction between age and initial antibiotic selection was the only interaction that achieved statistical significance. Although not statistically significant, the odds of treatment failure amongst patients with short duration of treatment (9 days or shorter) were more likely to experience treatment failure compared to those receiving long durations of 10 days or more (OR = 2.18 [95% CI: 1.59 to 2.99]). It should be noted that this outcome is likely influenced by effect modification; patients with exceptionally short durations of treatment (e.g., single doses) may distort the overall association between short durations and treatment failure.

Fox et al (2017)[418] published a mutli-center retrospective cohort study in women at least 16 years old with acute pyelonephritis defined as fever (≥39°C), rigots, or CVA tenderness in addition to pyuria (≥10 WBC/high-powered field), and significant bacteriuria ($\geq 10^5$ CFU/mL) with *Escherichia coli*. Patients were excluded for the following reasons: pregnancy, on dialysis, isolate not susceptible to treatment prescribed, polymicrobial urine culture, or ≥48 hours of antibiotic treatment prior to switch to the exposure drug. 81 women received 7 days of trimethoprim/sulfamethoxazole and 191 patients received 7 days of ciprofloxacin. 43% of all patients received IV antibiotics on day 1 of treatment. The likelihood of recurrent UTI within 30

days with TMP/SMX when adjusted for hospitalization and concomitant BSI was higher than with ciprofloxacin, though not statistically significantly so (adjusted OR = 2.3 [95% CI: 0.72 to 7.42]). Notably, this was also in the setting of fewer BSIs in the TMP/SMX group (9% vs. 21% in the ciprofloxacin group, $p < 0.01$). We agree with the authors of the study that suggest further prospective, randomized trials must be conducted to better assess the appropriate duration of treatment with TMP/SMX. While not statistically significant, the likelihood that the true OR is higher than 1 for the TMP/SMX group is notable and would not consider the results of this study to provide convincing support for the 7-day duration of TMP/SMX.

Fosse et al. (2022)[419] published a single center retrospective cohort study that included 29 patients with pyelonephritis who received TMP/SMX (10 received less than 7 days, 19 received 7 or more days). Unfortunately, all TMP/SMX patients were combined into a group with fluoroquinolones (the "first line recommended agents" group), so individual outcomes of the patients who received 7 versus more than 7 days of TMP/SMX are not known.

The cumulative available suggests that 7 days of TMP/SMX is likely adequate to treat pyelonephritis and UTIs caused by susceptible pathogens. However, a large RCT of TMP/SMX in this context would be necessary to enable a clear recommendation.

Fluoroquinolones

Based on the information presented in table 19 below, we are able to provide a clear recommendation for a duration of 5 days when using levofloxacin or ofloxacin and 7 days when using ciprofloxacin.

Table 19. Clinical and microbiological outcomes of RCTs directly comparing multiple fluoroquinolone durations for pyelonephritis.

RCT directly comparing multiple FQ durations for pyelonephritis (in chronological order)	FQ Arm 1 (dosing)	FQ Arm 2 (dosing)	Clinical cure comparison	Microbiologic cure comparison
de Gier et al.[420](1995) *n = 54*	Fleroxacin (400 mg IV daily for 3 days, THEN: 400 mg daily for 4 days, total 7 days)	Fleroxacin (400 mg IV daily for 3 days, THEN: 400 mg daily for 11 days, total 14 days)	n/a	4 to 6 weeks: 61% (7d) vs. 69% (14d), *p = NS*
Klausner et al.[119](2007) *n = 311*	Levofloxacin (750 mg daily for 5 days)	Ciprofloxacin (400 mg and/or 500 mg BID for 10 days)	Study days 15 to 19, mITT: 86.2% (10-14d after tx for LVX) vs. 80.6% (5-9d after tx for CIP); *RD* =	Study days 15 to 19, mITT: 83% (10-14d after tx for LVX) vs. 79.6% (5-9d after tx for CIP); *RD* =

			5.6 (95% CI: -4.9 to 16)	*3.4 (95% CI: -7.6 to 14.4)*
Peterson et al.[120](2008) *n = 1,109*	Levofloxacin (750 mg daily for 5 days)	Ciprofloxacin (400 mg and/or 500 mg BID for 10 days)	10 to 14 days, mITT: 82.6% (5-7d after tx for LVX) vs. 78.5% (0-2d after tx for CIP); *RD = 4.1 (95%CI: -10.4 to 2.1)* 15 to 22 days, mITT: 81.1% (10-17d after tx for LVX) vs. 80.1% (5-12d after tx for CIP); *RD = 0.9 (95%CI: -5.3 to 7.2)*	10 to 14 days, mITT: 79.8% (5-7d after tx for LVX) vs. 77.5% (0-2d after tx for CIP); *RD = 2.3 (95%CI: -8.8 to 4.1)* 15 to 22 days, mITT: 79.8% (10-17d after tx for LVX) vs. 79.8% (5-12d after tx for CIP); *RD = 0 (95%CI: -6.3 to 6.3)*
Sandberg et al.[405](2012) *n = 248*	Ciprofloxacin (500 mg BID for 7 days)	Ciprofloxacin (500 mg BID for 14 days)	10 to 14 days: 71 of 73 (97%) for 7d, 80 of 83 (96%) for 14d; *RD = -0.9% (95%CI: -6.5 to 4.8%)* 6 to 9 weeks: 68 of 73 (93%) for 7d, 78 of 84 (93%) for 14d; *RD = -0.3% (95%CI: -7.4 to 7.2%)*	n/a
Dinh et al.[404](2017) *n = 88*	Ofloxacin (200 mg BID for 5 days) OR Levofloxacin (500 mg daily for 5 days)	Ofloxacin (200 mg BID for 10 days) OR Levofloxacin (500 mg daily for 10 days)	10 days after treatment: 93% (5d) vs. 94.7% (10d), *p = NS* 30 days after treatment: 100% (5d) vs. 100% (10d), *p = NS*	30 days after treatment: 87% (5d) vs. 80% (10d), *p = NS*

β-lactams

There are multiple RCTs that compare various β-lactams against comparators from other classes (which were reviewed briefly in Section 3) or against other β-lactams for the same duration of treatment. The outcomes as it pertains to β-lactam use in the context of duration of treatment are reviewed below:

Hyslop and Bischoff (1992)[421] published a manuscript describing the outcomes of two RCTs that used either loracarbef or cefaclor as comparators. In total, 68 patients who received loracarbef and 25 patients who received cefaclor were considered evaluable. At "post-therapy" follow-up 5 to 9 days after conclusion of treatment, clinical cure (cure only, not including improved patients) for loracarbef group was 59 of 68 (86.8%) and the microbiological cure was 55 of 68 (80.9%). Clinical cure (cure only, not including improved patients) for the cefaclor group was 23 of 25 (92%) and the microbiological cure was 19 of 25 (76%). The minimum treatment duration was 14 days.

Sanchez et al. (2002)[422] published a randomized trial that included women 18 to 75 years old with a presumptive diagnosis of acute pyelonephritis. The following were excluded: pregnant women, patients with catheters, antibiotics within the last 7 days, renal impairment, UTI within the last 30 days, known functional or anatomical abnormalities of the GU tract. 54 women received 1 gram dose of IV ceftriaxone once daily (group A) while 51 received a 1 gram dose of ceftriaxone followed by oral cefixime once daily. Both groups completed 10 days of treatment based on susceptibility testing. The primary objective of this study was to assess short-term effectiveness of the two groups, thus clinical response after 3 days was the primary efficacy assessment. 52 of 54 (97%) in the IV ceftriaxone only group reported clinical cure or improvement compared with 50 of 51 (98%) in the oral transition to cefixime group; RD = -1%. At the 10-day follow-up visit, no patients made any complaint related to either the illness or treatment. Bacterial eradication after 3 days was 100% in both groups.

Wagenlehner et al. (2015)[423] published the ASPECT-cUTI study, a multi-center, international, randomized trial evaluating intravenous ceftolozane/tazobactam (C/T, 1.5 grams every 8 hours) compared with levofloxacin (750 mg daily) for 7 days. The study population consisted of patients 18 years of age or older with pyuria admitted to the hospital for either a complicated UTI or pyelonephritis. Of the 1,083 patients enrolled, 656 of them had pyelonephritis. In the entire modified ITT population, clinical cure (defined as complete resolution, substantial improvement, or return to preinfection signs and symptoms without need for additional antibiotic treatment) was achieved in 366 of 398 (92%) in the C/T group. In the entire modified ITT population, microbiological eradication (defined as a test-of-cure urine culture with fever than 10^4 CFU/mL of the baseline uropathogen) was achieved in 320 of 398 (80.4%) in the C/T group.

Rudrabhatla et al (2018)[424] published a small, pragmatic, non-inferiority (set NI margin = 15%) RCT at a single center in India investigating 7 vs. 14 day outcomes when using non-fluoroquinolone treatments for acute pyelonephritis. The study population included patients over 18 years old with acute pyelonephritis (measured or history of fever ≥38°C, dysuria, flank pain, costovertebral angle tenderness), urine microscopy showing ≥10 WBC/high-powered field or a

positive dipstick leukocyte esterase test, and pre-treatment urine culture with growth of a uropathogen with over 10^5 CFU/mL. Importantly, patients should have clinically improved following empirical or culture-guided antibiotic treatment and afebrile for over 48 hours at the time of randomization. "Complicated" patients were excluded (urinary catheterization, recurrent UTI history, anatomical abnormalities of the GU tract, prostatitis, severe sepsis or septic shock, pregnant/lactating women, patients on immunosupressive drugs). Only 11 of 27 patients in the truncated (7 day) group received a β-lactam alone, most others received them in combination with an aminoglycoside (amikacin). During the 6 week follow-up period, no patient in the truncated arm required retreatment, whereas 1 patient in the continued (14 day) treatment group was re-treated for recurrent UTI (RD = -3.7% [90% CI: -15.01 to 6.15]). When re-examined at a one-sided alpha of 2.5%, truncated treatment remained non-inferior based on the a priori defined NI margin of 15% (RD = -3.7% [95% CI: -18.28 to 9.52%]). Patients randomized to the truncated regimen had significantly lower hospital LOS (8 days vs. 14 days, $p < 0.001$). Since most β lactam containing regimens were combined with amikacin, it is challenging to extrapolate this small, underpowered RCT to patients who receive only a β-lactam for 7 days for pyelonephritis.

Lojanapiwat et al (2019)[425] published a randomized trial that compared the efficacy and safety of oral sitafloxacin with that of IV ceftriaxone followed by oral cefdinir for the treatment of acute pyelonephritis or complicated UTI. In this study, 112 patients with acute pyelonephritis were randomized to receive 2 grams IV ceftriaxone daily for 2-3 days followed by 200 mg oral cefdinir every 8 hours for an additional 4-12 days. The overall treatment duration was 7-14 days depending on patient response to treatment. The median duration of treatment was 3 days (IQR: 1 to 6 days) with initial ceftriaxone and 7 days (IQR: 1 to 23 days) for oral cefdinir. Clinical success (defined as resolution of symptoms and signs of pyelonephritis without need for additional antibiotic treatment) at end of treatment, 1 to 2 days after the last dose of study antibiotics, was achieved in 97 of 112 (86.6%) patients in the combined IV ceftriaxone/oral cefdinir group. In the entire cohort that received IV ceftriaxone/oral cefdinir (n = 148), microbiological success (defined as reduction of uropathogen(s) to less than 10^4 CFU/mL or presumed absence of uropathogen(s) based on clinical improvement if no urine sample was available) was achieved in 50% at end of treatment and 73% at end of study.

Table 20. Clinical and microbiological outcomes of RCTs directly comparing multiple β-lactam durations for pyelonephritis.

RCT directly comparing multiple β-lactam durations for pyelonephritis (in chronological order)	β-lactam Arm 1 (dosing)	β-lactam Arm 2 (dosing)	Clinical cure comparison	Microbiologic cure comparison
Ode et al.[406](1980)	Ampicillin	Ampicillin then pivampicillin	27 weeks after treatment	27 weeks after treatment

n = 34	(10 grams IV every 8 hours for 3 days THEN 10 grams IV every 12 hours for 4 days, total 7 days)	(Ampicillin 2 grams IV every 6 hours for 3 days THEN [ampicillin 2 grams IV every 6 hours OR 0.35 grams pivampicillin] TID for 4 days THEN 0.35 grams pivampicillin TID for 5 weeks, total 6 weeks)	initiation: 100% (7d) vs. 90.5% (6wk)	initiation: 23.1% (7d) vs. 42.9% (6wk)
Jernelius et al.[407](1988) *n = 77*	Pivampicillin (0.25g) and pivmecillinam (0.2g) combination product (2 tablets TID for 7 days)	Pivampicillin (0.25g) and pivmecillinam (0.2g) combination product (2 tablets TID for 7 days THEN 1 tablet TID for 14 days, total 21 days)	3 to 4 weeks after active treatment: 90.6% (7d) vs. 96.6% (21d), *p = NS*	3 to 4 weeks after active treatment: 28.1% (7d) vs. 71.4% (21d), *p = 0.004*
Mensa et al.[408](1999) *n = 304*	Ceftriaxone 1 g and/or cefixime 400 mg daily for 7 days	Ceftriaxone 1 g and/or cefixime 400 mg daily for 14 days	Unspecified follow-up time: 90.2% (7d) vs. 90.3% (14d), *p = NS*	Unspecified follow-up time: 78.9% (7d) vs. 75.2% (14d), *p = NS*

More observational studies that describe the clinical and/or microbiological results of various duration of β-lactam treatments for pyelonephritis exist as compared to the very few prospective randomized, controlled, comparative studies listed above. These observational studies are reviewed below (in chronological order):

Moustafa et al. (2016)[[426]] published a prospective, open, non-comparative, monocentric pilot study in 37 consecutive women between 18 and 65 years old (mean age = 32.8 years) who received a single dose of 1 gram ceftriaxone on the first day followed by 200 mg cefixime twice daily for 6 days for a total treatment duration of 7 days. On day 9, all patients were afebrile and 30 (81.1%) reported complete resolution of urinary symptoms. The other 7 patients reported clinical improvement. On day 30, no recurrence of UTI (defined as return of urinary symptoms) was observed in any of the patients. On day 9, only 3 of 37 (8.1%) urinary dipsticks were positive and all (100%) 37 of the cytobacterial examinations of the urine were negative (less than 10^5 CFU/mL).

Vogler and Pavich (2018)[427] published a retrospective review consisting of 55 adult female patients who were prescribed a cephalosporin for acute pyelonephritis and discharged from the emergency department. Four patients (3 cephalexin, 1 cefdinir) received 7 days of treatment, 43 (35 cephalexin, 8 cefdinir) received 10 days of treatment, and 8 (2 cephalexin, 6 cefdinir) received 14 days of treatment. There were no treatment failures, regardless of the prescribed duration. 43 of the 55 (78%) patients in the cephalosporin group received a single parenteral dose of ceftriaxone or an aminoglycoside prior to discharge.

Fosse et al. (2022)[419] published a single center retrospective cohort study that included 268 patients (median age: 39.5 years) with pyelonephritis who received cephalosporin (20 cefdinir, 190 cefpodoxime, 58 cephalexin) treatment for their acute pyelonephritis. 158 of 268 (59%) patients received at least one parenteral dose of antibiotics. The median duration of treatment for those who received cephalosporins was 10 days (IQR: 10 to 10 days). 35 (13%) patients received 7 days or less of a cephalosporin. Stratified outcomes for 7 days or less and more than 7 days were not available. The primary outcome was a composite of follow-up clinic, ED, or hospital visits/admissions due to UTI within 30 days from initial encounter. The primary outcome was attained in 44 of 268 (16%) of those prescribed cephalosporins.

Lin et al. (2022)[428] published a single center retrospective review describing 229 patients (89.5% female, mean age 42.4 years) discharged with cephalosporins (49 cephalexin, 115 cefuroxime, 64 cefpodoxime, 1 cefdinir) from the emergency department or observation unit. 212 of 229 (92.5%) received 1 or 2 doses of a parenteral antibiotic at initiation of treatment. 94.8% of patients received more than 7 days of treatment (median: 11 days, IQR: 9 to 12.5 days) The primary outcome of 30-day treatment failure (defined as the composite of one or more of: return to an ED or clinic with persistent symptoms, change in antibiotic due to persistent symptoms, or recurrence of UTI with the same organism) was seen in 35 (15.3%).

Overall, available data with the use of β lactams for pyelonephritis and by analogy to data supporting the treatment of Gram-negative bacteremia from a urinary source (see question 24) is sufficient to provide a clear recommendation for 7 days of treatment with certain caveats. Some of the RCTs that demonstrate comparable outcomes to other well-established treatments (e.g., fluoroquinolones) with 7 days of β lactams used IV treatment, stressing the importance of using β lactams and dosing with favorable pharmacokinetics that are likely to meet established PK/PD targets.

Aminoglycosides

There is insufficient evidence to suggest an optimal duration of treatment of acute pyelonephritis with aminoglycosides. Multiple observational studies exist describing the use of aminoglycoside monotherapy for the treatment of acute pyelonephritis, however there were no studies identified that specifically evaluated different durations of aminoglycosides for this indication.

Two published observational studies available look at either aminoglycoside monotherapy for the entire treatment course (Elbaz)[429] or for most of the treatment course (Zohar).[430]

Elbaz et al (2020)[429] published a retrospective propensity-matched cohort study of hospitalized patients at a single tertiary care center in Israel with acute pyelonephritis. They included patients aged 18 or older who were discharged from the internal medicine or geriatric departments with a diagnosis of pyelonephritis (fever, flank pain, tenderness, or WBC count $\geq 10^3$ cells/microliter with a positive leukocyte esterase or nitrite test and a positive urine culture with no other identifiable source) with or without BSI who received treatment within 2 days of the index urine culture. Neutropenic (ANC less than 500/microliter), pregnant, and dialysis patients were excluded. Patients with mixed bacterial growth on the index urine culture were also excluded. Aminoglycosides (36.5% amikacin or 63.5% gentamicin) were received by 715 patients (median age = 79 years, 46.7% male) as monotherapy. Patients who received aminoglycosides had significantly lower 30-day all-cause mortality than the comparators (non-aminoglycoside treatment); adjusted HR = 0.78 (95% CI: 0.65 to 0.95). The median total duration of antibiotic treatment was 4.5 days (IQR: 3 to 7 days). Notably, an elevated risk of AKI (defined as a doubling of serum creatinine from baseline) in patients who received aminoglycoside treatment for a median of 4.5 days was not detected (adjusted HR = 0.98 [95% CI: 0.97 to 1.004]). The number of recurrent hospitalizations within 3 months was lower in the aminoglycoside group (adjusted HR = 0.95 [95% CI: 0.91 to 0.99]), suggesting that approximately 5 days of treatment with an aminoglycoside alone may be safe and efficacious for acute pyelonephritis.

Zohar et al (2020)[430] performed a single center retrospective cohort study specifically in bloodstream infections from a urinary source caused by ESBL-producing Enterobacterales. As access to the bloodstream is often accomplished through the renal vasculature, it is reasonable to assume that most of the 193 patients (mean age = 79.3 years, 52.9% male) included in this study likely had pyelonephritis. Patients were excluded from the study if they died before receiving 48 hours of treatment, had other potential sources of BSI or polymicrobial BSI, or if the isolated pathogen was resistant to the antibiotic given. 74 patients received amikacin and 34 patients received gentamicin, the majority of which (77.8%) had an estimated creatinine clearance over 60 mL/min. The median legnth of appropriate antibiotic treatment was 8 days (IQR: 7 to 10 days) and the median length of treatment with an aminoglycoside was 7 days (IQR: 6 to 9 days); as such, most patients who received an aminoglycoside would have outcomes largely attributable to those drugs. All aminoglycoside patients received once daily dosing, however precise dosing was not provided in the manuscript. The primary safety outcome was AKI at 14 days after presentation. The authors assumed that treatment switch (off of aminoglycosides) may have prevented some AKI events, so a combined outcome of AKI or treatment switch due to toxicity or safety concerns was used. Using the composite outcome, there were numerically more events in the aminoglycoside group than in the carbapenem or piperacillin/tazobactam group (20 vs. 9, respectively), but this difference was not statistically significant (RD = -7.8% [95% CI: -17.67 to 2.07]). It would be reasonable to assume that the reputation of aminoglycosides for causing AKI may lead clinicians to prematurely switch patients off aminoglycoside treatment to an alternative that is perceived to be safer, thus overestimating the true incidence of AKI attributable to aminoglycoside treatment. When evaluating only clinically observed AKI events (defined per the KDIGO criteria of over 50% increase or over 0.3 mg/dL [26 μmol/L] increase from baseline), the groups appear similar (13 vs. 9, respectively); RD = -1.32% (95% CI: -10.35 to 7.7). Neither 30-day all-cause mortality (primary outcome) nor recurrence of bacteriuria within 90 days were statistically significantly different between the aminoglycoside and carbapenem or piperacillin/tazobactam groups. Together, similar to the study by Elbaz et al, this hypothesis-

generating study suggests it is possible that aminoglycoside monotherapy is safe and effective when given for up to 7 days for acute pyelonephritis.

Wie et al (2014)[431] conducted a single center (South Korea) retrospective review of 274 patients with pyelonephritis who all received gentamicin monotherapy for initial treatment. Duration of gentamicin monotherapy was between 6 and 7 days, depending on the specific subgroup. Duration of total antimicrobial therapy was approximately 14 days. As such, initial gentamicin only accounted for approximately 50% of the total treatment duration, making it challenging to draw conclusions about its effectiveness in this setting, especially given the heterogeneity in the choice of oral antimicrobials. Reassuringly, 98.7% of patients with pyelonephritis and an organism susceptible to gentamicin experienced defeverscence within 5 days, as would be expected. Additionally, AKI was extremely rare occuring in only 3 of the 274 patients. This study may provide some additional reassurance that initial treatment with an aminoglycoside would result in initial clinical improvement and is safe from a renal perspective; whether these outcomes would remain consistent if the patients did not receive an average of 7 additional days of antimicrobials is not known.

More rigorous, prospective, controlled studies of aminoglycoside monotherapy should be conducted to further define the role of this class of antimicrobials in treatment of pyelonephritis, especially in the context of increasing antimicrobial resistance. However, given the risks of nephro- and oto/vestibular toxicity with complete courses of therapy, prescribing aminoglycosides for more than several days poses an undesirable risk and should likely be done with shared decision making with patients. These potential toxicities also underscores the need for additional prospective studies on optimal duration of treatment.

Fosfomycin

Four RCTs and a cohort study are informative to the potential for fosfomycin therapy as a treatment for pyelonephritis.

Wald-Dickler et al (2021) published a retrospective cohort analysis of outcomes of patients with complicated UTI (pyelonephritis or cystitis in the setting of catheters, stones, or obstruction) treated with oral transitional fosfomycin (110 patients, 48 [44%] with pyelonephritis, 7 [6.4%] with bacteremia) versus continued parenteral ertapenem (212 patients, 139 [66%] with pyelonephritis, 82 [38.7%] with bacteremia) across three public hospitals in Los Angeles county, California.[432] The large majority of infections (90%) were caused by ESBL-producing *E. coli* or *Klebsiella* spp. resistant to other oral options. Oral fosfomycin was dosed at 3 grams daily, every other day, or every third day. There were no observed difference in clinical success at 30 days (65.4% in fosfomycin group vs. 74.1% in ertapenem group, $p = 0.1$) or at last follow up, and no difference in relapse rates. However, patients treated with oral transitional fosfomycin had shorter lengths of hospital stay (average 1.4 days less, $p = 0.002$) and less adverse events than those treated with IV ertapenem (1 vs. 10 events, respectively; $p = 0.06$). Neither duration of IV lead-in therapy (OR = 1.01 [95% CI: 0.92 to 1.11]), nor frequency of dosing of fosfomycin were associated with success/failure rates.

In 2019, Kaye et al. published the results of the ZEUS trial, a multi-center, non-inferiority (NI margin = 10%) RCT of IV fosfomycin (referred to as ZTI-01) compared to IV piperacillin/tazobactam therapy (intermittent dosing, each dose given over 1 hour) for 465 patients with complicated UTI.[240] Acute pyelonephritis was the primary diagnosis for 100 (54.3%) patients in the fosfomycin group and 96 (53.9%) in the piperacillin/tazobactam group. 19 (10.3%) patients in the fosfomycin group had bacteremia at baseline compared with 13 (7.3%) patients in the piperacillin/tazobactam group. Patients were treated for 7 days, or up to 14 days (at the investigators' discretion) if they had concomitant bacteremia. IV fosfomycin was found to be non-inferior to piperacillin/tazobactam for the primary efficacy outcome of overall success (defined as clinical success and microbiologic eradication) at test-of-cure visit at day 19-21 (64.7% vs. 54.5%; RD = 10.2% [95% CI: -0.4 to 20.8%]). Clinical response rates were high in both groups (90.8% for fosfomycin vs. 91.6% for piperacillin/tazobactam; RD = -0.8% [95% CI: -7.2 to 5.6%]).

Sojo-Durado et al (2022) published a multi-center, pragmatic, open label, non-inferiority (NI margin = 7%) RCT describing 143 patients with bacteremic UTI due to multidrug-resistant *E. coli*.[433] Patients were randomized to receive IV fosfomycin (70 participants) or a comparator (ceftriaxone or meropenem if resistant; 73 participants) with the option to switch to oral fosfomycin for the fosfomycin group or an active oral drug or parenteral ertapenem for the comparator group after 4 days. The median Pitt score was 1 in both groups. Patients received an average of slightly more than 5 days of IV lead in to complete a total course of therapy of10-14 days. Eighty-six percent of patients in the fosfomycin arm were transitioned to oral therapy to complete therapy, while 66% of patients in the standard of care arm were orally transitioned. Clinical and microbiological cure rates in the modified intention-to-treat population were 68.6% in the fosfomycin group and 78.1% in the comparator group; RD = -9.4% (one-sided 95% CI: -21.5% to ∞); fosfomycin was found to be not non-inferior based on the NI margin of 7%. However, there were fewer clinical or microbiological failures in the fosfomycin arm (14.3% for fosfomycin vs. 19.7% for comparator; $p = 0.19$). The excess overall failures in the fosfomycin arm were driven by inability to complete therapy due to intolerability of the antimicrobial therapy (8.5% for fosfomycin vs. 0% for comparator; $p = 0.006$).

Ten Doesschate et al (2022) published a multi-center, non-inferiority (NI margin = 10%) RCT in 15 Dutch hospitals with febrile UTI due to *Escherichia coli*.[434] Bacteremia was present at baseline in 25 (52.1%) patients in the fosfomycin group compared with 25 (51%) in the ciprofloxacin group. A presumptive diagnosis of acute pyelonephritis was recorded for 18 (37.5%) patients in the fosfomycin group and 17 (34.7%) in the ciprofloxacin group. After 2 to 5 days of IV lead-in treatment, the patients were transitioned to either oral fosfomycin or ciprofloxacin to complete a total duration of 10 days of treatment. If used as part of the IV lead-in, IV fosfomycin was dosed at 3 grams daily while patients transitioned to oral fosfomycin were dosed at 3 grams every 48 hours. Criteria for clinical cure was met in 36 (75%) patients in the fosfomycin group and 30 (65.2%) patients in the ciprofloxacin group; RD = 9.6% (95% CI: -8.8 to 28%); fosfomycin was found to be non-inferior to ciprofloxacin. Microbiological cure was observed in 29 (78.4%) patients in the fosfomycin group compared with 33 (94.5%) patients in the ciprofloxacin group; RD = -16.2% (95% CI: -32.7 to 0%). More patients randomized to oral fosfomycin reported gastrointestinal adverse events (52.1% for fosfomycin vs. 30.4% for ciprofloxacin; RD = 20.8% [95% CI: 1.6 to 40%]).

Finally, Seo et al (2023) published the results of a multicenter, randomized, controlled, open-label, non-inferiority (NI margin = 15%) RCT comparing oral transition to fosfomycin vs. continued IV (carbapenem or BL/BLI) therapy in 93 patients with complicated UTIs caused by ESBL-producing Enterobacterales.[435] Initial clinical diagnosis included pyelonephritis in 16 (33%) patients in the fosfomycin arm compared with 13 (29%) in the continued IV treatment arm. Bacteremia was present in 11 (23%) patients in the fosfomycin arm and 13 (29%) in the continued IV treatment arm. Eligible patients were randomized on hospital day 4 to 7 to one of the two treatment arms and continued treatment for a total of 10 days. The primary endpoint was clinical resolution of UTI related signs and symptoms within 4 days of ending treatment. The primary endpoint was achieved in 45 (93.8%) patients in the fosfomycin group and 43 (95.6%) patients in the continued IV treatment group; RD = -1.8% (95% CI: -10.9 to 7.3%); transition to oral fosfomycin was found to be non-inferior to continued IV treatment based on the NI margin of 15%. Similar to other RCTs, more patients who received oral fosfomycin reported gastrointestinal side effects (10.4% for fosfomycin vs. 2.2% for continued IV treatment).

Collectively these results provide a high degree of confidence that oral fosfomycin dosed daily, every other day, or possibly every 3 day is effective in treating complicated UTIs. However, there may be less certainty regarding the reliability of oral fosfomycin for more systemic UTIs such as pyelonephritis and bacteremic UTIs owing to the heterogeneity of trial designs, variable non-inferiority margins, and the difficulty for some patients to complete the requisite treatment course due to gastrointestinal side effects. As such, a clear recommendation for fosfomycin duration of treatment for pyelonephritis cannot be made.

Febrile UTI.

van Nieuwkoop et al (2017) published the FUTURIST trial[436], a pragmatic, non-inferiority (NI margin = 10%) RCT conducted in 35 primary care centers and 7 EDs in the Netherlands. 200 patients were randomized to either 7 or 14 days of treatment for a febrile urinary tract infection (fUTI). Overall, short-term clinical cure, defined as being alive with absence of fever and resolution of UTI symptoms with no additional antimicrobial therapy prescribed, (through the 10 to 18-day post-treatment visit) in the intention to treat population was 90.4% in the 7-day group compared with 94.9% in the 14-day group (RD = -4.5% [90% CI: -10.7 to 1.7%]). In the per-protocol population, short-term clinical cure occured in 90.2% in the 7-day group and 94.6% in the 14-day group (RD = -4.3% [90% CI: -10.8 to 2.1%]). In both cohorts, the lower bound of the 90% CI falls below –10%, thus should be interpreted as 7 days being not non-inferior to 14 days. In the ITT population, long-term clinical cure (termed “cumulative efficacy”, reflecting the endpoint assessed at 70 to 84 days post-treatment visit) was 92.6% in the 7-day group and 91.5% for the 14-day group (RD = 1.1% [90% CI: -5.5 to 7.6%]). In the PP population, long-term clinical cure was 92.4% in the 7-day group and 90.8% in the 14-day group (RD = 1.6% [90% CI: -5.3 to 8.4%]). Short-term bacteriological cure was lower in the 7-day group in both the ITT (92.5% [7d] vs. 96.7% [14d]; RD = -4.3% [90% CI: -9.7 to 1.2%] and PP (92.3% [7d] vs. 96.5% [14d]; RD = -4.2% [90% CI: -9.9 to 1.4%]) populations. Subgroup analyses based on biological sex also found biological males to have lower short-term clinical cure rates (RD, men versus women = -11.2% (90% CI: -20.6 to –1.8), but not long-term cure rates (RD, men versus women = 0.9% [90% CI: -8.6 to 10.3%]). Unfortunately, definitive conclusions are limited as the

study was originally supposed to recruit 200 patients per arm but only achieved 97 and 103 subjects in the 7 and 14-day groups, respectively. A non-inferiority study which does not achieve the pre-planned sample size is most likely to arrive at a “not non-inferior" conclusion as this study did for some of the outcomes.

Edlund et al (2022) published a multi-center, open-label RCT based out of 12 Swedish hospitals including 152 patients with suspected or diagnosed febrile UTI randomized to receive either IV temocillin or IV cefotaxime.[437] Participants were treated for 7-10 days (or up to 14 days at the discretion of the investigators if the patient had concomitant bacteremia). Subjects who showed clinical improvement could be switched to an oral antibiotic on or after day 4 of antimicrobial treatment. The primary aim of the study was to investigate the disturbance of gut microbiota, however clinical and bacteriological outcomes were included as non-inferiority secondary endpoints. The median duration of IV temocillin or IV cefotaxime was 3 days (IQR: 1 to 10 days for temocillin and IQR: 1 to 6 days for cefotaxime). 51 patients in each group transitioned to oral ciprofloxacin to finish treatment. Only 1 patient in each group continued IV temocillin or IV cefotaxime for their entire treatment course. Early (after 3 days of treatment: 97.1% and 93.7%) and late (7 to 10 days after all antibiotic treatment finished: 96.7% and 91.5%) clinical response was extremely high in both groups with no therapeutic failures. Early (after 3 days of treatment: 98.2% and 98%) and late (7 to 10 days after all antibiotic treatment finished: 90.7% and 79.2%) bacteriological response was also high in both groups. This suggests that 7 to 10 days of treatment for febrile UTI is likely sufficient.

Lafaurie et al (the PROSTASHORT study group) published an RCT in 2023[114] that concluded treatment with 7 days of ofloxacin for fUTI in men was inferior to 14 days of treatment. The primary outcome was treatment success, a composite defined as a negative urine culture and the absence of fever and of subsequent antibiotic treatment between the end of treatment and 6 weeks after day 1. The absolute risk difference was –21.9% (95%CI -33.3 to -10.1%] and inferiority was still demonstrated in clinical success with -4.3% (95%CI −9.8 to −1.3%). However, several flaws in study design and interpretation must be considered. First, the trial included the whole spectrum of fUTI in men except those with septic shock or an indwelling urinary catheter. Notably, the trial is named PROSTASHORT and patients with prostatic pain on rectal examination were eligible for enrollment. As long as prostatic abscess was not detected on ultrasound, it seems that patients with prostatitis were included in the study. Second, the antibiotic used in the trial was ofloxacin at a dose of 200 mg twice daily, the FDA and EMA licensed dose. Ofloxacin is the racemic mixture of L- and D-enantiomers, with all antimicrobial activity in the L-enantiomer. In most countries, ofloxacin has been largely replaced by the L-enantiomer, levofloxacin. While the standard dose of levofloxacin in a patient with normal renal function is 500 to 750 mg daily, the study used a dose of ofloxacin equivalent to only 100 mg twice daily of levofloxacin. Of note, despite this very low dose of levofloxacin-equivalent, 96% of patients treated with short course therapy achieved clinical resolution of signs and symptoms at end of therapy, indicating a very high rate of clinical success. The primary outcome was largely driven by excess asymptomatic bacteriuria in the short course group at follow up, with no difference in late relapse. Given the lack of difference in relapse, having ASB at late follow up is of no clinical significance. Overall, the possible inclusion of patients with prostatitis, use of doses far below the equivalent usual levofloxacin dose, and the treatment failures being driven by ASB without clinical relapse substantially limits the generalizability of the findings.

Q23: What is the appropriate duration of treatment for catheter-associated urinary tract infections (CAUTI)?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

The optimal duration of antimicrobial therapy for CAUTI has not been rigorously evaluated in large RCTs.[243] Data are limited to observational studies or small subgroups of RCTs evaluating complicated UTIs, so a clear recommendation cannot be made. Based on available observational data, 5 to 7 days appears as effective as longer treatment courses and represents a reasonable duration of treatment for most cases of CAUTI in conjunction with catheter exchange and/or removal, if possible.[247] No existing data demonstrate an association between longer courses and improved patient outcomes.

Overall summary

The optimal duration of antimicrobial therapy for a catheter-associated urinary tract infection (CAUTI) is unclear, and it is very likely that a "one size fits all" approach does not hold, even in the light of the several manifestations potentially included in this definition, from cystitis to pyelonephritis with and without bacteremia.[438] Previous IDSA guidelines from 2010 have suggested a variable duration from 3 to 14 days, with longer durations advised in cases of "delayed clinical response."[213]

While not supported by high quality evidence, it is a reasonable premise that a catheter should be removed if it is no longer clinically indicated or needed. If the catheter is indicated, an exchange to remove biofilm and to provide a non-colonized culture specimen seems appropriate, particularly if the catheter has been in place for more than 1-2 weeks as colonization rates approach 100% by that time. The theoretical benefit of catheter exchange should presumably be balanced against any risks or challenges anticipated with the procedure, particularly in individuals with challenging anatomy or recent ureteric trauma. This approach was tested in a small randomized controlled trial (RCT) which included 54 older adult nursing home residents with long-term indwelling catheters (days from last replacement ranging from 17 to 37) and a diagnosis of CAUTI.[243] Participants were randomized 1:1 to either catheter replacement or no replacement before starting a course of antimicrobials lasting 14 days (fluoroquinolones as empiric choices, changing to alternative effective agents in case of resistant strains). The replacement group had significantly lower rates of polymicrobial bacteriuria at day 28, a shorter time to afebrile status and clinical improvement, and a lower rate of CAUTI at 28 days post-treatment.

In a small RCT conducted in 1987[439], among 46 patients with an intermittently catheterized neurogenic bladder, a 10-day course of antibiotic therapy was not superior to a 3-day course for the outcomes of cure, persistence, relapse, or reinfection. This study is too small to support any claims of non-inferiority and is also limited by the inclusion of asymptomatic bacteriuria (59% of patients in the 3-day group vs. 45% in the 10-day group). Unfortunately, in many high-quality

studies, CAUTI or presence of an indwelling catheter represented exclusion criteria; however, in some RCTs a limited number of CAUTI were included.

For instance, Peterson et al. led a non-inferiority RCT[120] enrolling 619 subjects with a definitive diagnosis of acute pyelonephritis or complicated urinary tract infection with an isolated pathogen comparing 5 days of levofloxacin vs. 10 days of ciprofloxacin; however, only 68 (11%) were catheterized. No granular data for CAUTI is presented for the clinical response. As compared to those without CAUTI, microbiologic eradication was statistically significantly lower; however, among these subjects, microbiologic eradication rate was higher in the levofloxacin/short-course group (30/38, 79%) than it was in the ciprofloxacin/long-course group (16/30, 53%); RD = 25.6% (95% CI: 3.6 to 47.7%). Additionally, in the van Nieuwkoop et al (2017)[436] study discussed in question 22, an indwelling catheter was only reported in 3 (3%) and 2 (1.9%) patients, respectively which precludes the ability to make any inferences.

With respect to observational evidence, a population-based retrospective cohort study[247] obtaining data from administrative datasets in Canada included 4,436 non-hospitalized patients aged 66 and older with presumed CAUTI, defined as urine culture positivity associated with antibiotic prescription in a subject with urinary catheterization documented within the prior 90 days. The outcome of interest was treatment failure, a composite of repeat urinary antibiotic prescribing, positive blood culture with the same organism, all-cause hospitalization, or mortality within 60 days. Several antibiotics of different classes were compared. Concerning duration, the range 5-7 days was set as referent. An adjusted analysis was conducted adjusting for potential confounders of age, sex, Charlson comorbidity score, acute care, and long-term care days in the last 12 months. Longer courses (8-14 days) were not associated with better outcomes (adjusted RR = 1.05 [95% CI: 0.99 to 1.11]), whereas shorter courses (less than 5 days) were associated with higher likelihood of treatment failure (adjusted RR = 1.15 [95% CI: 1.05 to 1.27]).

Overall, available data in this subset of patients is limited, but by analogy to pyelonephritis (question 22) and Gram-negative bacteremia (question 24), a maximal duration of 7 days is likely sufficient. Whether shorter or longer durations may be applicable in CAUTI, or even within different subsets of CAUTI patients, remains to be demonstrated in high-quality, reproducible studies. Thus, we are unable to provide a clear recommendation at this time.

Q24: What are optimal oral agents and an appropriate duration of treatment for Gram negative bacteremia from a urinary source?

Clear Recommendation

Executive summary

Multiple randomized, controlled trials comprised of patients with Gram-negative bacteremia from predominantly from urinary sources demonstrate non-inferiority of 7 compared to 14 total days of treatment for a variety of patient-oriented outcomes, such as clinical cure, clinical failure, relapse, and all-cause mortality.[414–416,440] Thus, we can provide a clear recommendation for 7 days of treatment for Gram-negative bacteremia from a urinary source when source control has

been addressed (if applicable). Whether shorter durations might also be effective is unknown as they have not been studied. These trials tested duration as a strategy and not specific drugs; thus, while no specific class of medications can be recommended, it is also reasonable to ensure that the choice of drug and the doses used are optimized for the patient and a urinary focus of infection.

Overall summary

Historical practices surrounding the duration of treatment of Gram-negative bloodstream infections (BSI) were poorly defined with a large range of treatment durations. However, three relatively recently published RCTs and an individual patient data meta-analysis thereof allows the authors to make a clear recommendation about duration of therapy. The authors acknowledge that none of the RCTs reviewed below can entirely exclude an important mortality difference as they all used a composite endpoint. However, the forthcoming BALANCE randomized trial[441] is powered on mortality and will add important context to this discussion.

First, Yahav, et al. (2019)[414] was one of the first randomized controlled trials to investigate noninferiority of a short duration of 7 days compared to longer historical durations (14 days) of antibiotics for gram-negative BSI. The primary outcome was assessed at 90 days post-randomization and was a composite of all-cause mortality, clinical failure, and readmission or extended hospital stay and the pre-defined non-inferiority margin was 10%. Most patients in the study had bacteremia from a urinary source (68%) and the main pathogens were Enterobacterales (89.9%). Patients without source control were excluded from this study. Most patients in both arms received an IV cephalosporin and 65% of patients in the short arm compared to 81% of patients in the long arm transitioned to oral therapy (most commonly with a fluoroquinolone). The trial found that 7 days of therapy was non-inferior to 14 days, with the primary composite outcome occurring in 45.8% and 48.3% patients respectively (RD = -2.6% [95% CI: -10.5 to 5.3%]).

Next, von Dach and colleagues (2020)[416] investigated the clinical effectiveness of C-reactive protein (CRP)-guided, 7-day and 14-day durations for Gram-negative bacteremia. They conducted a multicenter, noninferiority, point-of-care randomized clinical trial and randomized patients to one of the previously mentioned treatment groups to assess clinical failure rates at days 30, 60 and 90 after treatment initiation. Most patients in the study had BSI from a urinary source (65%). The primary outcome was the clinical failure rate at day 30, defined as the presence of at least 1 of the following: recurrent bacteremia, local suppurative complication, distant complication, restarting Gram-negative directed antibiotic treatment due to clinical worsening suspected to be due to the initially defined pathogen, or death due to any cause. The pre-specified non-inferiority margin was 10%. The primary outcome occurred in 11 of 166 (6.6%) patients in the 7-day group and 9 of 163 (5.5%) patients in the 14-day group. difference in 7-day vs 14-day group. The risk difference between the 7-day and 14-day groups was 1.1% (1-sided 97.5% CI: -∞ to 6.3). By day 60, clinical failure occurred in 16 of 157 (10.2%) patients in the 7-day group and 12 of 158 (7.6%) patients in the 14-day group; RD = 2.6% (1-sided 97.5% CI: -∞ to 8.9%). By day 90, clinical failure occurred in 16 of 151 (10.6%) in the 7-day group and 16 of 153 (10.5%) in the 14-day group; RD = 0.1% (1-sided 97.5% CI: -∞ to 7%).

The third and most recent RCT published evaluating 7 days of treatment for Gram-negative BSI was conducted by Molina, et al (2022)[415] in Spain similarly aimed to determine if 7 days was non-inferior to 14 days for bloodstream infections caused by Enterobacterales. The enrolled 248 patients (55% with suspected urinary source of BSI) evaluating for the primary outcome of clinical cure, relapse of infection, and relapse of fever with a pre-defined non-inferiority margin of 10%. A desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR) analyses were also performed to compare the efficacy and safety together for each treatment duration. In the ITT population, relapse of BSI occurred in 7 of 108 (6.5%) patients in the 7-day group compared with 6 of 121 (5%) in the 14-day group; RD = 1.5% (1-sided 97.5% CI: -∞ to 8.4%). Relapse of fever occurred in 21 of 110 (19.1%) in the 7-day group and 23 of 119 (19.3%) in the 14-day group; RD (ITT population) = -0.2% (1-sided 97.5% CI: -∞ to 10.1%). Absence of clinical cure occurred in 8 of 110 (7.3%) in the 7-day group and 12 of 122 (9.8%) patients in the 14-day group; RD (ITT population) = -2.6% (1-sided 97.5% CI: -∞ to 5.1%). Death (from any cause) occurred in 3 of 119 (2.5%) patients in the 7-day group and 9 of 129 (7%) patients in the 14-day group; RD (ITT population) = -4.5% (1-sided 97.5% CI: -∞ to 1.2%).

Table 21. Proportion of patients included in published RCTs evaluating 7 vs. 14 days of treatment for Gram-negative bacteremia who received oral β-lactams or had urine source of bacteremia.

RCT	Proportion that received oral β-lactams		Proportion with urine source of bacteremia	
	7-day arm	*14-day arm*	*7-day arm*	*14-day arm*
Yahav et al.[414](2019)	14.3%	20.7%	69.3%	66.8%
von Dach et al.[416](2020)	Not reported	Not reported	63%	71%
Molina et al.[415](2022)	Not reported	Not reported	59.3%	51.2%

An individual participant data meta-analysis of these 3 trials has subsequently been published specifically looking at the Enterobacterales.[440] Using that data as a starting point, we specifically evaluated the endpoints of 90-day mortality, 30-day mortality, and 30-day relapse of bacteremia in the subgroup of patients with UTI using a restricted maximal likelihood model random effects meta-analytic relative risk and the overall control event rate (Figures 1 to 3). For 90-day mortality in UTI patients, the absolute risk difference with 7 vs. 14 days of therapy was -0.6% (95%CI -6.4 to 14.3%); for 30-day mortality, -0.1% (95%CI -2.4 to 5.7%), and for 30-day relapse 0.8% (95% CI: -1 to 5%). This analysis is post hoc and in a limited subgroup with unbalanced sample sizes. Nonetheless, it is the most comprehensive analysis possible with the currently available data.

Figure 1. Forest plot for 90-day mortality in published RCTs evaluating 7 vs. 14 days of treatment for Gram-negative bacteremia.

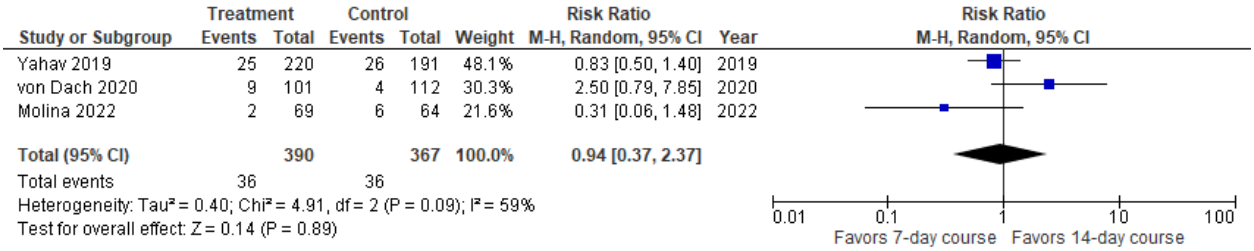


Figure 2. Forest plot for 30-day mortality in published RCTs evaluating 7 vs. 14 days of treatment for Gram-negative bacteremia.

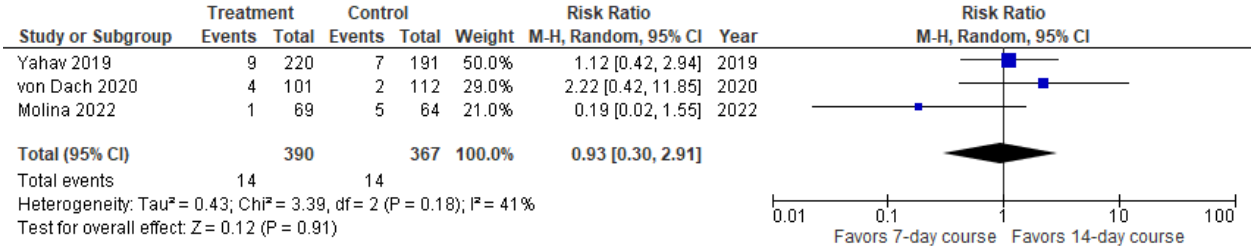
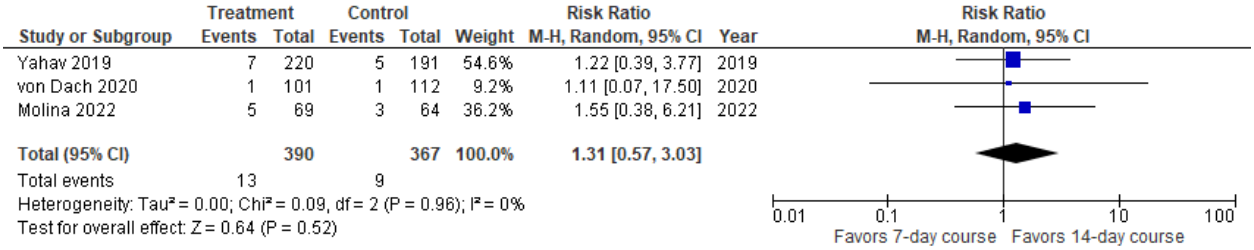


Figure 3. Forest plot for 30-day BSI relapse in published RCTs evaluating 7 vs. 14 days of treatment for Gram-negative bacteremia.



Several observational studies have evaluated shorter compared with longer durations of treatment for Gram-negative BSI, however, for methodological reasons (where multiple quality RCTs exist) observational studies of treatment duration for bacteremia can be misleading and do not meaningfully add to the discussion in the view of the authors of this guideline.[442] As previously alluded to at the beginning of this question, the forthcoming BALANCE randomized trial will provide much needed additional context.[441]

We acknowledge that the data presented on febrile UTI in question 21 adds additional uncertainty when viewed in the context of the 3 RCTs presented in this question that demonstrate non-inferiority of 7 days to 14 days for Gram-negative bacteremia, especially in the context of biologically male patients. As was discussed in question 21, there are numerous possible explanations attributable to study design for the findings in FUTURIST and PROSTASHORT that could explain the conclusions that are inconsistent with the aforementioned RCTs in Gram-negative bacteremia. Notably, FUTURIST only achieved approximately half of the a priori defined sample size in each group, making it much more likely for the study to arrive at a "not non-inferior" conclusion.[436] In PROSTASHORT, as long as prostatic abscess was not observed on ultrasonography, the patients remained eligible for inclusion in the study. Inclusion of patients with prostatitis and use of a suboptimal dose of ofloxacin (equivalent to only 100 mg twice daily of levofloxacin) both may contribute significantly to the observed lower rates of treatment success with 7 days of treatment. Again, the definition for the outcomes results in a very

important nuance to the results of PROSTASHORT. The primary outcome of "treatment success" included both clinical and microbiological cure components; it would appear that a very high proportion (96%) of patients in the short course group experienced a cure of clinical symptoms, but many had asymptomatic bacteriuria at follow-up, thus causing them to not achieve the a priori defined treatment success criteria. It should be noted that there was a very high rate of clinical cure and no difference in late relapse in the short course group.[114] The multicenter, open-label RCT of patients with suspected or diagnosed febrile UTI published by Edlund et al. (2022) observed similarly high rates of clinical response (94-97% 3 days after treatment ended and 92-97% 7 to 10 days after treatment ended); most patients were expected to receive between 7 and 10 days of total treatment however the 57 (38%) patients with bacteremia could have received up to 14 days based on historical practice at the included institutions. No descriptive statistics on total duration of treatment was available and it should be noted that the primary purpose of this study was not to compare durations of treatment for febrile UTI, but instead the effects of two different antimicrobials on the microbiome.[437]

Table 21 demonstrates that the majority of patients in the 3 RCTs that concluded non-inferiority of 7 to 14 days in Gram-negative bacteremia had a likely urine source and older men made up 52.8% (median age: 71 years)[414], 39.2% (median age: 79 years)[416], and 52.6% (median age: approximately 66 years)[415] of the study populations. However, the study designs of the 3 Gram-negative BSI trials may have been more likely to consistently exclude patients with prostatitis and other infections that may necessitate longer durations of treatment. For example, Yahav et al. (2019) excluded patients with fever or hypothermia that was measured in the 48 hours prior to recruitment and those perceived to have an uncontrolled focus of infection.[414] Similarly, von Dach et al. (2020) excluded patients with fever in the 24 hours prior to recruitment, recurrent bacteremia within 60 days, and/or those with "complicated infections."[416] Lastly, Molina et al. (2022) excluded patients with bacteremia secondary to "other infectious foci that require prolonged antimicrobial treatment" and bacteremia focus not controlled at time of inclusion and not expected to be controlled in the following 24 hours.[415] It seems reasonable to assume that patients with prostatitis are much more likely to have fever, have recurrent infections with similar or the same organisms within a short period of time, and/or be considered "complicated" or perceived to have an uncontrolled source of infection. In comparison, PROSTASHORT excluded patients with antibiotic treatment for a UTI in the last 12 months which likely excluded some patients with prostatitis, but also many without prostatitis. FUTURIST only excluded patients with renal abscess, underlying chronic prostatitis, and/or presence of metastatic infectious foci.

The likely reality is that patients with febrile UTI and Gram-negative bacteremia lie on a spectrum; some with comparably "uncomplicated" infections (e.g., pyelonephritis) that are likely to experience favorable clinical outcomes when a duration of 7 days is used and some who may have another focus of infection or an uncontrolled source that may warrant longer treatment durations (e.g., acute prostatitis). Rather than blanketly applying a 7-day duration for all febrile UTI or Gram-negative bloodstream infections, sufficient patient work-up should aim to demonstrate with as much certainty as possible the probability of additional foci or sources of infection that must be accounted for and treated. Determining whether or not the findings of published RCTs apply to each individual patient relies on the assumption that a sufficiently appropriate and comprehensive work-up has been completed.

While the existing data does not allow us to provide a clear recommendation for Gram-negative bacteremia from a urinary source, there are several important considerations to maximize the chances of a good outcome. Observational studies seeking to define the association between certain antimicrobial selections and clinical outcomes often seek "highly bioavailable" antimicrobials as ideal candidates for transitioning to oral treatment.[443–446] Bioavailability of a drug is defined as the extent and rate at which the active moiety enters systemic circulation and can be taken out of context when applied to the treatment of infectious diseases.[447–449] Administration of an antimicrobial results in a specific range of expected drug concentrations in plasma (and the infected tissues) and these drug concentrations are more important than simply the proportion of the drug that makes it to systemic circulation. This is an especially (and perhaps uniquely) important distinction when treating infectious diseases. Antimicrobial plasma levels (regardless of the specific bioavailability) should be interpreted in the context of the minimum inhibitory concentration (MIC) to determine if established or proposed pharmacokinetic and/or pharmacodynamic targets, which have been associated with positive clinical outcomes are achieved.[450–452]

Table 22 below contrasts the oral second-generation cephalosporin cefprozil with a bioavailability of over 90%, which one could reasonably call "highly bioavailable" with the oral third generation cephalosporin cefpodoxime with a bioavailability of only 30-50%.

Table 22. Pharmacokinetic comparison between oral cephalosporins with varying bioavailability and likelihood of target attainment when used for Gram-negative bacteremia.[453]

	Cefprozil	**Cefpodoxime**
Bioavailability	94% (high)	30-50% (low-medium)
Plasma C_{max}	18.3 mcg/mL (1,000 mg)	3.8 mcg/mL (400 mg)
Half-life	1.2 hours	2.7 to 4.2 hours
Reported MIC_{90} vs. *Escherichia coli*	8 mcg/mL	1 mcg/mL
Estimated %fT>MIC_{90} (goal: 60-70% for cephalosporins vs. Gram-negative organisms)	Dosed 500 mg twice daily: **Approximately 12%**	Dosed 400 mg twice daily: **Approximately 50%**

When selecting an oral agent, bioavailability is only one piece of the puzzle to consider. The wild-type distribution of pathogen MICs and actual antimicrobial concentrations achieved in vivo and at the site of infection should be evaluated, if possible, with selections reflecting those with the highest chance to achieve target attainment associated with positive treatment outcomes. A consensus statement published by Heil et al (2021) provides further discussion using a modified Delphi process on proposed dosing for oral β-lactams in the setting of Gram-negative BSI.[454]

Q25: What are potential treatment option(s) and appropriate durations of treatment for asymptomatic bacteriuria in populations in which treatment is indicated?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

Unnecessary treatment of asymptomatic bacteriuria (ASB) risks side effects without benefit and represents low value care and poses a threat to antimicrobial sustainability.[455–459] There is no conclusive evidence that there is any population in which treatment of ASB is required and randomized controlled trials are welcomed. There are theoretical reasons and limited evidence which support treatment of ASB in pregnant patients[162,460] and in those undergoing invasive urologic procedures associated with expected mucosal bleeding.[461–464] When treating ASB, the ideal duration of treatment is unknown. In pregnancy, it may be reasonable not to exceed the duration used for symptomatic cystitis (e.g., 3-5 days, depending on the antimicrobial used). For patients undergoing invasive urologic procedures, most authors feel that many patients could receive a single dose of pre-operative prophylaxis prior to the scheduled procedure.

Overall summary

Asymptomatic bacteriuria (ASB) is a common and most often benign finding in many populations including healthy women, residents in long-term care facilities, and subjects with urinary tract abnormalities.[107,457,465] The exact level of bacteriuria of when to treat ASB, if indicated, is not truly known. The IDSA 2019 update to the Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria defines ASB as the presence of 1 or more species of bacteria growing in the urine at specified quantitative counts ($\geq 10^5$ colony-forming units per mL) irrespective of the presence of pyuria and in the absence of clinical signs and symptoms attributable to urinary tract infection.[107] The references supporting this cut-off date back to 1956, when Dr. Edward Kass described that 95% of those whom the diagnosis of pyelonephritis was made or suspected had 10^5 CFU/mL of urine; however, it is notable that a few had as low as 10^2 CFU/mL.[167] Over time, the cut-off of 10^5 CFU/mL has become entrenched as a standard definition of bacteriuria, but there have been concerns regarding the sensitivity of the cut-off in symptomatic patients, whereby patients with symptoms with lower than 10^5 CFU/mL may be missed.[142,165] Conversely, in the context of a truly asymptomatic patient, there are advantages to using higher cut-offs and limiting a definition to known uropathogens, as this would lead to fewer patients being labelled as having ASB. Evidence has demonstrated that in most cases ASB treatment not only does not confer any significant benefit but may also increase the risk of selecting antimicrobial-resistant pathogens[455], of paradoxically increasing the risk of future symptomatic UTI[107,457], or lead to *Clostridioides difficile* infections[107,458,459]; therefore, a strategy which avoids routine antimicrobial treatment is considered preferable.

There has been a substantial ongoing debate about the categories for which antibiotic therapy should be offered. No conclusive benefit has been demonstrated for subjects without risk factors, postmenopausal women, patients with diabetes mellitus, older adult institutionalized patients, patients prior to joint replacement, subjects with recurrent urinary tract infections, and patients after kidney transplantation (KT).[107,466]

With specific respect to kidney transplant patients, a recent meta-analysis of five randomized controlled trials[467] (including a total of 566 patients) comparing antibiotic therapy with no

treatment of ASB in recipients of KT showed no significant difference between treatment of ASB versus no treatment concerning patients' and graft' outcomes, such as graft function (3 studies, mean difference = -0.04 [95% CI: -0.14 to 0.07]), hospitalization due to UTI (3 studies, RR = 0.88 [95% CI: 0.37 to 2.11]), and symptomatic UTI (5 studies, RR = 1.05 [95% CI: 0.78 to 1.41]). Since high-quality data are scarce in the early post-transplantation period (in the first two months), some caution is be needed when extrapolating data for all KT recipients with ASB, but there is no compelling evidence to screen and treat this category for ASB, particularly those who will already be receiving months of TMP/SMX prophylaxis for opportunistic infections.

There are two specific populations where there may be more potential for benefit and for whom many clinicians would choose to treat ASB. Specifically, these are pregnant women and patients prior to undergoing invasive urologic procedures associated with mucosal bleeding and trauma (e.g., transurethral surgery of the prostate or the bladder, or percutaneous stone surgery).[107,468] These will be discussed in more detail below:

Pregnancy.

A 2019 Cochrane review evaluated the potential benefit of treating ASB in pregnant women in RCTs and quasi-RCTs.[469] A total of 15 studies were identified including more than 2000 subjects. All but one were considered at risk of bias. In 12 studies including 2,017 women that reported the incidence of pyelonephritis, the relative risk was 0.24 (95%CI 0.13 to 0.41). Only one study was published after 1990. The overall control event rate was 19.9%, and so this would correspond to an absolute risk reduction of 15.1% (95%CI 11.7% to 17.3%; NNT 7 95%CI 6-9). There were also reductions in preterm birth (RR 0.34; 95%CI 0.13-0.88; 3 studies including 327 women) and of low birthweight babies (RR 0.64; 95%CI 0.45-0.93; 6 studies; 1437 babies). The United States Preventive Services Task Force also published a similar review of ASB in general, but including pregnant women and arrived at very similar (almost identical) numbers.[162]

While these effect sizes seem impressive, there has been a substantial improvement in pre- and peri-natal care since 1960 to 1990. Using PubMed, we were unable to identify any new RCTs published since 2015. The only modern study by Kazemier et al (2015)[470] generates significant equipoise by challenging both the relevance of ASB screening, and when present, its treatment to pyelonephritis and low birth weight. They randomized 40 pregnant women with ASB to nitrofurantoin and 45 to placebo while enrolling 163 untreated ASB-positive and 4,035 ASB-negative women in a paired prospective observational study. All were uncomplicated pregnancies. The combined rates of pyelonephritis, preterm labor, or both were 2.5% in the nitrofurantoin group, 2.9% in the placebo and untreated ASB positive groups combined (Risk Difference nitrofurantoin vs. untreated -0.4%; 95%CI -3.6% to 9.4%), and 1.9% in patients without ASB (adjusted OR for ASB vs. no ASB = 1.5; 95%CI 0.6-3.5).

Taken together, it is understandable why risk averse clinicians and patients may decide to screen for and/or treat ASB; however, there is substantial equipoise both based on the data and the observation that several European countries do not have ASB screening programs. A large, multinational, active and placebo-controlled trial powered on pyelonephritis and neonatal outcomes would represent a significant contribution. A nested question of duration within such a large platform trial would also be helpful.

If one is choosing to treat ASB in pregnancy, there are limited comparative effectiveness data on which agents should be preferred and for what duration. In the 2019 Cochrane review,[469] there was inadequate evidence to demonstrate that any duration was superior to another as compared to no therapy. A more specialized Cochrane review specifically addressing duration of ASB therapy in pregnancy was published in 2015.[471] This review summarized results of 13 RCTs published from 1975 to 2009, enrolling 1622 women, and comparing single-dose antibiotics with short-course (from four to seven days) treatment. In 10 of 13 RCTs, the same antimicrobial agent was used. Single dose vs. long-course (14 days) or continuous (until delivery) therapy strategies were not evaluated. Outcomes included (among others) "no cure" (RR 1.28; 95%CI 0.87-1.88; 13 studies including 1502 women); pyelonephritis (RR 3.09 (95%CI 0.54 to 17.55; 2 studies including 102 women); preterm delivery (RR 1.17; 95%CI 0.77-1.78; 3 studies including 804 women); low birthweight (RR 1.65 95%CI 1.06-2.57; 1 study of 714 women) and side effects (RR 0.70; 95%CI 0.56-0.88; 12 studies including 1460 women). We were unable to identify any new RCTs on PubMed after 2009. Overall, the certainty of the evidence is low. If one accepts that ASB in pregnancy needs to be treated in the first place, the available evidence is most in favor of a duration similar to cystitis acknowledging an increased risk of side effects but potentially better efficacy than a single dose.[471–473]

In terms of choosing any one regimen over another, in the absence of compelling evidence of efficacy, treatment choices should consider availability, cost, safety profile, trimester of pregnancy, and culture results. Reasonable oral options, sorted alphabetically, might include: amoxicillin, amoxicillin-clavulanate, ampicillin, cefadroxil or cephalexin, cefuroxime, fosfomycin, nitrofurantoin, pivmecillinam, or trimethoprim/sulfamethoxazole (trimester dependent).[474]

There is little to no evidence of how to manage asymptomatic MDRO bacteriuria in pregnancy. Because of the challenges in accessing appropriate therapy, or in a limited safety profile in pregnancy, it might be preferrable to obtain a catheter specimen to confirm that the result does not represent contamination and, if so, to have a multidisciplinary conference with experts in infectious diseases and infectious diseases pharmacy. One might consider single dose aminoglycoside therapy in such cases, if susceptible as these drugs have decades of experience in pregnancy, concentrate in the urinary tract, and reserve novel or restricted agents for subsequent infections.[474,475]

Patients undergoing invasive urologic procedures.

A concern surrounding this subgroup of patients is the admixture of blood with urine containing a significant bacterial load. This is hypothesized to come with some risk of subsequent febrile UTI or more serious infective complications including disseminated infection (bacteremia) and sepsis. Despite inclusion in existing guidelines as discussed below, there is limited evidence on which to inform a decision as to the appropriate duration of treatment and authors feel it is reasonable to point out that individualized risk assessments may vary based on patient-specific factors and the type of procedure being performed. Additionally, although only supported by observational evidence, authors believe it is reasonable to utilize recent urine culture data to

“target” routine antimicrobial prophylaxis for urological procedures against recently identified organisms within the GU tract.

The IDSA guideline on ASB published in 2019[107] generally suggests a short-course treatment (one or two doses) based on low-quality evidence, administering therapy 30-60 minutes before the procedure. The weak recommendation is based on three studies in the setting of transurethral resection of the prostate (TURP) including two RCTs[462,476] and a third observational study[463], reviewed below:

One RCT published in 1984 by Grabe et al.[461] compared cefotaxime to no therapy in patients undergoing transurethral resection of the prostate (TURP). A total of 96 patients were randomized, of whom 47 received cefotaxime (1 gram every 12 hours for 3 doses after Foley catheter removal) and 49 received no therapy. While not totally representative of the question at hand, all 4 cases of bacteremia (2 intervention and 2 control, same pathogen as urine) and 6 cases of upper tract infection (1 intervention, 5 control) occurred in the group with preoperative asymptomatic bacteriuria (21 intervention and 29 control patients). While post hoc, this corresponds to 3/21 cases in the intervention group and 7/29 in the control group for a risk difference of -9.9% (95%CI -31.5% to 11.7%). Overall, this study suggested that the benefit, if any, of antibiotics might be realized in those with pre-operative bacteriuria.

The other RCT cited by the existing IDSA guideline was conducted by Grabe et al in 1987[462] compared three strategies in patients undergoing transurethral resection of the prostate (TURP): oral ciprofloxacin from the day before operation until catheter removal, oral ciprofloxacin for five days after catheter removal and no antimicrobial treatment. Asymptomatic bacteriuria was present in 45-61% of patients. All infectious complications occurred in patients with bacteriuria detected preoperatively. These included 1 case of upper tract infection in each of the ciprofloxacin arms (1 of 76 and 1 of 75, respectively corresponding to 1 of 46 and 1 of 34 with pre-operative bacteriuria) versus 3 cases of sepsis with bacteremia, one culture negative sepsis, and 4 cases of upper tract infection in the untreated group (8 of 71 in the group, or 8 of 38 in those who had bacteriuria). Post hoc calculations imply rates of 2/80 (2.5%) vs. 8/38 (21.1%) corresponding to a risk difference of -18.6% (95%CI -32.0 to -5.1%). This small study provides limited RCT level evidence to support the hypothesis that treatment of ASB at the time of TURP could reduce post-operative infectious complications.

The third study cited by the existing IDSA guideline is a retrospective cohort study performed in Turkey that included 70 consecutive patients with symptomatic bacteriuria who underwent one of several different urological procedures, most commonly a double J stent insertion and/or exchange.[463] The included patients were divided into two groups based on the duration of antibiotic prophylaxis they received; group A received a “short course” defined as 1 to 2 doses starting 30-60 minutes before the procedure started while group B received a “long course” defined as 3 to 15 days of treatment before and/or after the specified procedure. During the study period, zero patients in the “short” nor “long” group developed infectious complications, such as sepsis or upper urinary tract infection. The authors concluded that a single dose prior to the procedure may have similar effectiveness in preventing infectious complications from urological procedures when comparing to longer courses.

A best practice statement issued by the American Urological Association (AUA) in 2020[464] details proposed procedure-associated risk probability of surgical site infection as well as recommended antimicrobial prophylaxis regimens for a variety of urologic procedures. Notably, the authors of the AUA statement suggest using a single dose prior to the procedure as the duration of prophylaxis for nearly all procedure types.

Taking all evaluable RCTs, the meta-analyses have been conducted comparing short (defined as 24 hours or less of duration, including single dose regimens) and longer (greater than 24 hours duration) durations of antimicrobial prophylaxis for urologic procedures (Figure 4-7). RCTs comparing two durations within the same category were excluded.

Figure 4. Forest plot of RCTs evaluating short (≤24 hours) or longer (>24 hours) duration of prophylaxis with the outcome of any reported infectious complication, including SSIs and urinary tract infections (a positive urine culture was not considered an infectious complication).[477–495]

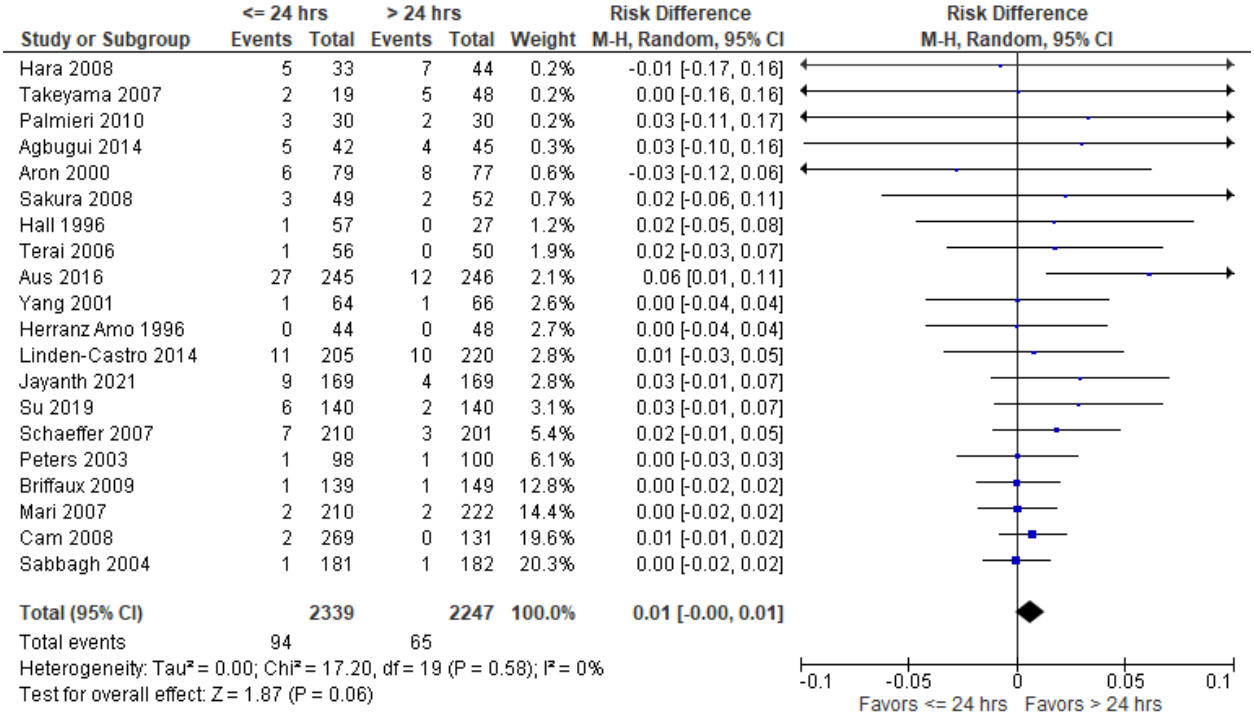


Figure 5. Funnel plot of RCTs evaluating short (≤24 hours) or longer (>24 hours) with the outcome of any reported infectious complication, including SSIs and urinary tract infections (a positive urine culture was not considered an infectious complication).[477–495]

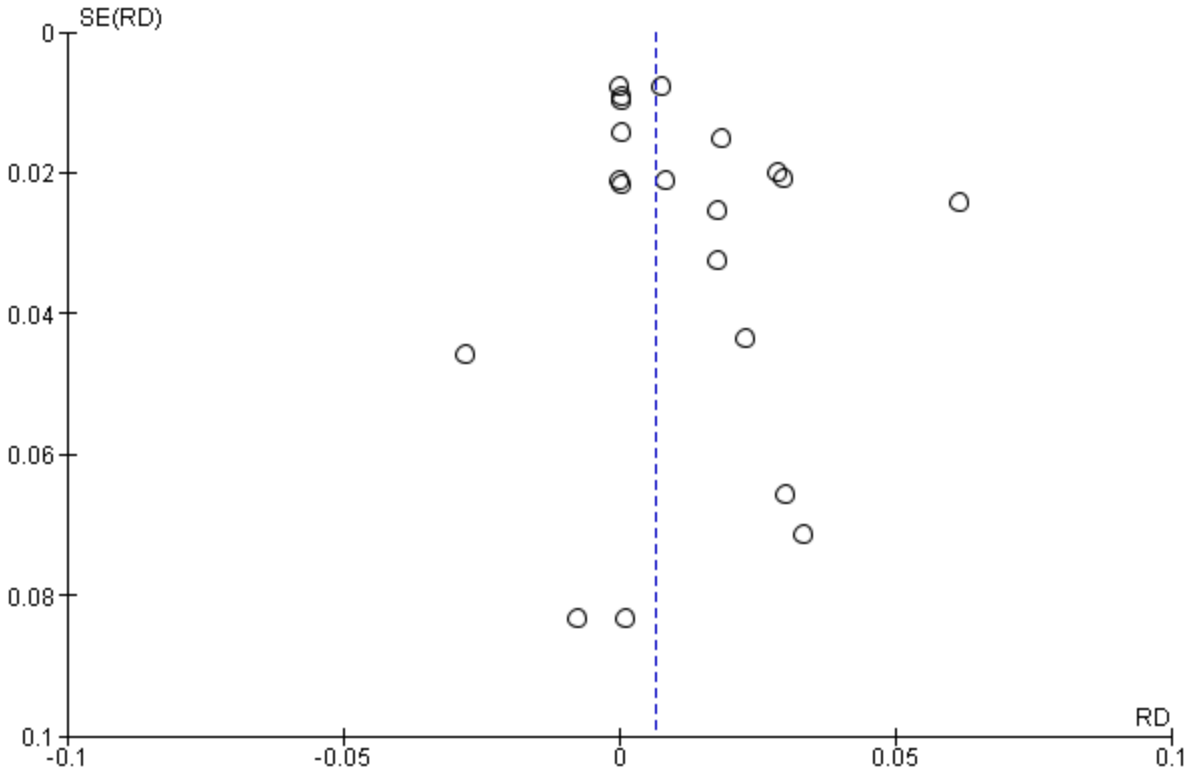


Figure 6. Forest plot of RCTs evaluating short (≤ 24 hours) or longer (>24 hours) duration of prophylaxis with the outcome of reported symptomatic urinary tract infection (a positive urine culture without symptoms does not qualify as an event).[477,480,482,485,488,490,492,494]

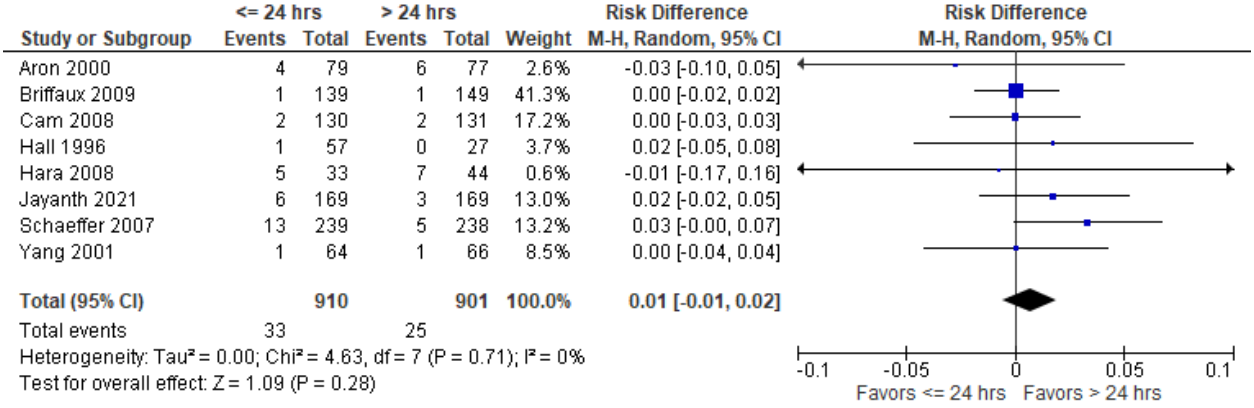
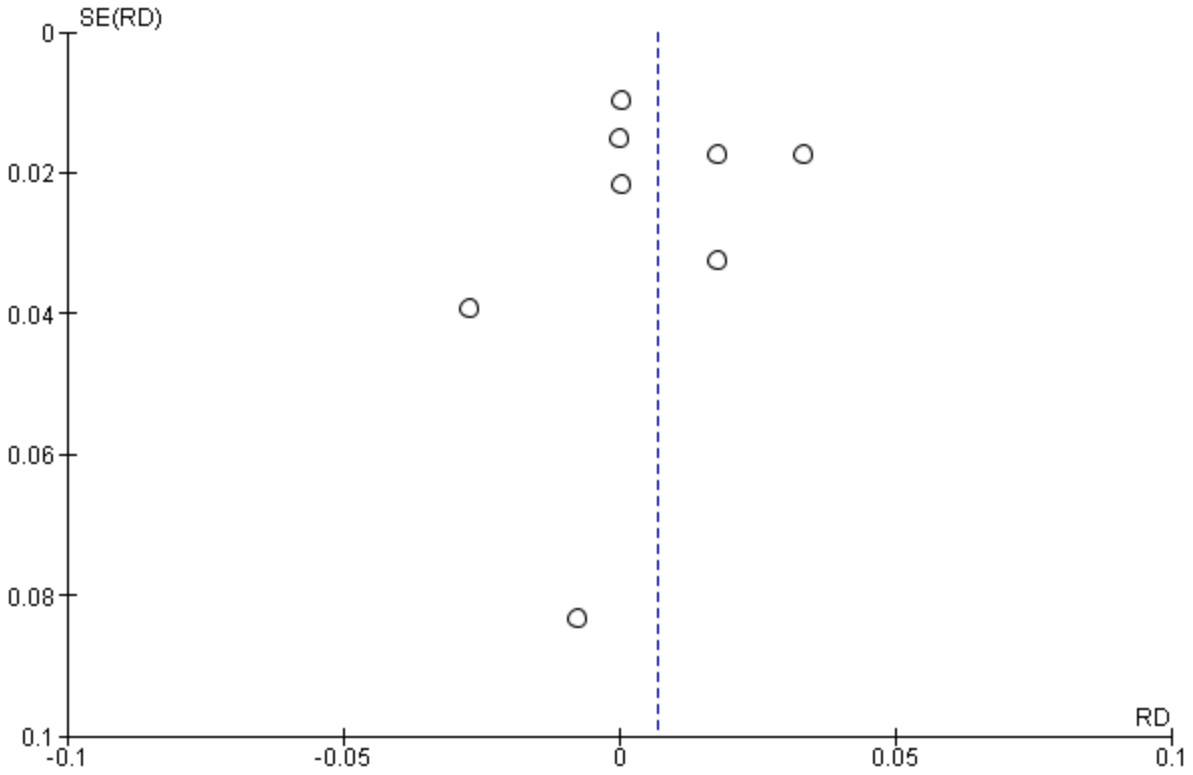


Figure 7. Funnel plot of RCTs evaluating short (≤24 hours) or longer (>24 hours) duration of prophylaxis with the outcome of reported symptomatic urinary tract infection (a positive urine culture without symptoms does not qualify as an event).[477,480,482,485,488,490,492,494]



Collectively, the data above suggest that a single dose of prophylaxis is likely reasonable for most patients with ASB undergoing an invasive urologic procedure as there does not appear to be a difference in the rates of symptomatic UTI when comparing 24 hours or less of prophylaxis with longer than 24 hours of prophylaxis (RD = 1% [95% CI: -1 to 2%], $p = 0.28$). Differences with regard to any infectious complication when comparing the same two groups approached statistical significance (RD = 1% [95% CI: -0 to 1%], $p = 0.06$), but may be driven by inherent risks associated with procedures and not the duration of antimicrobial prophylaxis. Data for other potential outcomes of interest (e.g., sepsis) are limited to very few trials. It is plausible that patients with particularly complex cases due to anatomy, prosthesis, or other factors may warrant a modified approach (e.g., longer than 24 hours of prophylaxis).

Q26: What are potential treatment option(s) and duration of treatment for urinary tract infections caused by multi-drug resistant organisms (MDRO)?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

The potential treatment option(s) depend on the organism identified and specific resistance mechanisms. No data exist to suggest that the duration of treatment for urinary tract infections caused by multidrug-resistant organisms (MDROs) needs to be modified in comparison to those caused by non-resistant organisms. Authors feel it is reasonable to determine a treatment duration based on the anatomical location and clinical severity (e.g., cystitis or pyelonephritis) as well as the clinical response to treatment provided that: the antimicrobial being used has demonstrated

activity against the organism, the antimicrobial has proven or a high likelihood of efficacy for treatment of urinary tract infections, and any applicable source control has been obtained.

Overall summary

Difficult-to-treat (DTR) Pseudomonas aeruginosa

Definitions of *Pseudomonas aeruginosa* isolates with varying levels of antimicrobial resistance are often used interchangeably, however for the purposes of this document, note the following definitions. Multidrug-resistant (MDR) *P. aeruginosa* is defined as *in vitro* resistance to an anti-Pseudomonal drug in at least 3 of the following drug classes: penicillins (e.g., piperacillin/tazobactam), cephalosporins (e.g., ceftazidime), fluoroquinolones, carbapenems, and aminoglycosides.[257,496] Difficult-to-treat (DTR) *P. aeruginosa* is defined as *in vitro* resistance to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.[219,257,497] MDR and DTR P. aeruginosa isolates are often the result of a variety of complex, often coexisting mechanisms of resistance.[498,499] The unique combinations of resistance mechanisms can make interpretation of resistance phenotypes challenging. *P. aeruginosa* ranks as the 2nd most common CAUTI pathogen reported to NHSN from 2018 to 2021 in pediatrics and as the 3rd most common CAUTI pathogen in adults.[500] In the absence of catheterization and/or repeated healthcare or antimicrobial exposure, *P. aeruginosa* is a generally uncommon urinary pathogen.[501]

Potential treatment options for cystitis due to DTR *P. aeruginosa* include:

- Aminoglycosides

  The data surrounding the use of a single dose of an aminoglycoside for the treatment of cystitis was discussed in question 21. Although *P. aeruginosa* was under-represented (only 2% of all isolates) in the studies included in the systematic review[230], the pharmacokinetic principles remain sound and it represents a reasonable option for cystitis due to DTR *P. aeruginosa.* This may represent a particularly appealing option for patients who do not otherwise have indications for hospital admission. As depicted by table 23, there are no longer interpretive criteria for gentamicin as of January 2023. Additionally, clinical breakpoints for tobramycin have been lowered and amikacin only now has interpretive criteria for infections due to *P. aeruginosa* from a urine source from CLSI and EUCAST. Plazomicin does not have any interpretive criteria available, however based on available descriptive *in vitro* susceptibility data, it would not be expected to provide efficacy if the isolate is resistant to other aminoglycosides.[502]

Table 23. Available interpretive criteria for antimicrobial susceptibility testing of aminoglycosides.

	CLSI[503]			EUCAST[504]			USCAST[505]		
Interpretation	***S***	***I***	***R***	***S***	***I***	***R***	***S***	***I***	***R***
Tobramycin	≤ 1	2	≥ 4	≤ 2		≥ 4	≤ 1		≥ 2
Interpretation	***S***	***I***	***R***	***S***	***I***	***R***	***S***	***I***	***R***
Amikacin	≤ 16*	32*	≥64*	≤ 16*		≥ 32*	≤ 2		≥ 8
Gentamicin	None								

Plazomicin	None

** Urine breakpoint only*

- β lactams and BL/BLI combinations

Ceftolozane/tazobactam[409], ceftazidime/avibactam[506], imipenem/cilastatin/relebactam[507,508], and cefiderocol have been shown to be non-inferior to "best available" or "standard of care" treatments in randomized trials that included urinary tract infections and the use of these agents for cystitis caused by DTR *P. aeruginosa* is reasonable.

Several "real world" observational studies[509–512] and a systematic review[513] describing the use of ceftolozane/tazobactam provides additional reassurance that use of the drug in clinical practice appears to result in outcomes consistent with those found in the ASPECT-cUTI trial[409]. These studies also provide additional context in the diverse populations in which ceftolozane/tazobactam is typically used in (e.g., immunocompromised patients, patients with APACHE II scores as high as 40, etc.).

Additional observational studies are available for ceftazidime/avibactam.

More published observational studies are available for imipenem/cilastatin/relebactam.

Observational studies describing cefiderocol use

- Oral fosfomycin

Fosfomycin presents a convenient, effective treatment option for other resistant organisms (e.g., ESBL-producing *Escherichia coli*), however the prevalence of the *fosA* gene is notably much higher in *Pseudomonas aeruginosa* than other Enterobacterales.[514] Several other proposed intrinsic fosfomycin resistance mechanisms have been documented within *Pseudomonas aeruginosa* as well.[515] In RCTs conducted with single dose oral fosfomycin (see question 20), *P. aeruginosa* has been under-represented, limiting generalizability of those studies to infections due to the pathogen, especially DTR *P. aeruginosa*. Additionally, in a dynamic bladder infection model with synthetic human urine, single and multiple doses of oral fosfomycin were not effective despite exposure to higher-than-average urinary concentrations and daily dosing for 7 days. Pre-exposure high-level resistance was detected in 11 of 16 isolates. Notably, emergence of resistance still occurred despite high levels.[516] Several *in vitro* studies have suggested fosfomycin may be useful in combination with other classes of antimicrobials and warrants additional research.[517–520]

- Colistin or polymyxin B

Prior to the invent of new β lactams and BL/BLI combinations, colistin (and polymyxin B) were one of the only options available for the treatment of multidrug resistant Gram-negative pathogens.[521,522] Since, colistin has been used alone or in combination in the "best available" or "standard of care" treatment arms for new antimicrobials being evaluated in the context of UTIs due to MDROs including DTR *P. aeruginosa*.[507]

A small prospective, observational cohort study of 33 patients (24 with cystitis and 9 with pyelonephritis) evaluated clinical, bacteriological, and safety outcomes of using colistin for UTI due to drug resistant *P. aeruginosa*.[523] The average CCI score was 4.9 and 48.5% of

the patients had a urinary catheter. While 10 (30.3%) patients met criteria for sepsis, only 4 (12.1%) had concomitant bacteremia. The average colistin treatment duration was 8.31 days with a mean daily dose of 5 million IU (2.21 mg CBA/kg/day). In patients who received colistin monotherapy, clinical cure (defined as absence of symptoms or as consistent improvement in signs and symptoms was 89.5% and microbiological eradication was achieved in 76.9%. The timing in which the outcomes were assessed was not able to be determined. The rate of AKI by the end of treatment was high (30.3%).

A single center, propensity score-adjusted and matched cohort study published by Montesinos et al (2022) evaluated clinical and microbiological outcomes in patients treated with aminoglycoside (amikacin) or colistin (CMS) monotherapy (compared with other antibiotic treatments, most commonly β lactams) for complicated urinary tract infections due to drug resistant *P. aeruginosa*.[524] Baseline Pitt score in patients with concomitant bacteremia (4 of 48 patients, 8.3%) was 2 in the amikacin/CMS group compared with 1 in the other antibiotic treatments group. 22.9% of patients in the amikacin/CMS group and 39.6% of patients in the other treatments group met criteria for sepsis or septic shock. The duration of treatment of each group was not available in the main or supplemental manuscripts. In the propensity-matched cohort, early clinical failure (at day 7) was 28.7% in the amikacin/CMS group compared with 37.7% in the other antibiotic regimens group; adjusted OR for clinical failure at day 7 = 0.53 (95% CI: 0.18 to 1.58). Microbiological clearance was lower in the amikacin/CMS group (51.4% vs. 78.6%; adjusted OR = 0.43 [95% CI: 0.14 to 1.36]), but the significance of these findings are unclear since rates of relapse and reinfection were lower in the amikacin/CMS group (for relapse: 12.5% vs. 22.6%; crude OR = 0.49 [95% CI: 0.17 to 1.42] and for reinfection: 20.8% vs. 26.4%; crude OR = 0.73 [95% CI: 0.29 to 1.85]). Surprisingly, rates of any acute kidney injury were lower in the amikacin/CMS group (18.8% vs. 34%; crude OR = 0.45 [95% CI: 0.18 to 1.13]).

Despite concerns about limited urinary concentrations, polymyxin B has similar documented rates of clinical success compared to colistin in multiple observational cohort studies of patients with MDR Gram-negative UTIs, with lower observed rates of nephrotoxicity.[525–528]

There is currently no evidence to support the prolongation of therapy, beyond typical recommendations for treatment duration for urinary tract infections caused by DTR *P. aeruginosa*. If a patient has clinically responded to empiric treatment for cystitis, but results of antimicrobial susceptibility testing reveal that the selected empiric agent is not active against the causative organism, we agree with the current consensus guidance that recommends against changing empiric therapy, extending treatment courses, or repeating urine cultures to document clearance.[219] If a patient with a systemic infection (e.g., febrile or bacteremic UTI, pyelonephritis, or BSI from a urinary source), most authors believe it to be most reasonable to change to an agent with demonstrated *in vitro* activity via AST and begin an evidence-based duration of therapy starting from the first date of active treatment.

Carbapenem-resistant Acinetobacter baumannii (CRAB) and Stenotrophomonas maltophilia

Urinary tract infections caused by *Acinetobacter* spp. and *S. maltophilia* are rare, typically healthcare acquired, and often catheter associated UTIs (CAUTI).[529–531] CDC data in their 2018

to 2021 HAI Pathogens and Antimicrobial Resistance Report show in adults, *Acinetobacter* spp. as the 14th most common CAUTI pathogen in hospital wards and intensive care units (ICUs) and the 9th most common in long-term acute care hospitals (LTACHs).[500] In pediatrics, *Acinetobacter* spp. is the 15th most common CAUTI pathogen in all location types.[500] *S. maltophilia* is an even rarer cause of UTI with literature limited to case reports.[529] No prospective clinical trials have evaluated antibiotic treatments or durations specifically for UTIs caused by CRAB and *S. maltophilia*. Furthermore, caution must be taken in assessing these data, as they do not clearly distinguish true infection from ASB. Given that these pathogens are uncommon causes of UTIs outside the setting of indwelling catheters, catheter removal or exchange is likely the primary therapeutic intervention to achieve source control, and selection of antibacterials and duration of therapy may be of secondary importance (see question 23).

Combination therapy for severe CRAB and *S. maltophilia* infections is often used due to the limited number of active antibiotics, lack of clear effectiveness of any single antibiotic, and poor outcomes. However, multiple clinical studies[532–540] and a meta-analysis[541] have not demonstrated the superiority of combination therapy over monotherapy for either pathogen. Unfortunately, few (if any) patients with UTIs were included in these studies and conclusions were limited by low-quality data, bias, and heterogeneity. Based on available data, we cannot provide a clear recommendation on whether or not to use a combination treatment approach for either CRAB or *S. maltophilia* infections. The primary role of combination therapy empirically is to ensure that at least 1 of the agents is active against the etiologic bacteria; there is no evidence that dual active therapy results in superior outcomes to monotherapy. Most WikiGuidelines authors agree it is reasonable to take clinical severity into account when deciding on how many potentially active agents are being used empirically. In patients with more severe pyelonephritis and/or hemodynamic instability, combination therapy may be warranted, particularly until clinical improvement is observed. For patients with localized cystitis or CAUTI, monotherapy could be considered, particularly for a drug with demonstrated *in vitro* susceptibility that attains high urine concentrations.

CRAB and *S. maltophilia* UTIs may be less severe compared to other infections. In large cohort studies of patients with CRAB, positive urine cultures were associated with lower mortality compared to other sites.[542,543] More generally, prospective cohort studies of patients with MDR Gram-negative infections have shown greater clinical success and lower mortality for UTIs compared to other infectious sources.[525,544] Furthermore, antibiotics that concentrate in the urine may retain clinical activity even with in vitro resistance. Use of such antibiotics as monotherapy may be effective for CRAB and *S. maltophilia* UTIs.

For the few CRAB isolates that remain susceptible to standard therapies for UTIs, such as the fluoroquinolones and trimethoprim/sulfamethoxazole, these inexpensive, highly effective regimens are logical treatment options. However, surveillance studies show low susceptibility of CRAB isolates to these agents.[545] Other treatments that have not been supported by prospective clinical trial data specifically for CRAB UTI, but may be effective based on foundational principles of antimicrobial therapy, data from studies evaluating their use in treatment of UTIs from other organisms or infectious sources, and *in vitro* activity may include:

- Ampicillin/sulbactam

Meta-analyses have demonstrated that sulbactam-based regimens are associated with better outcomes for CRAB infections compared with other regimens, however very few UTIs were included in these studies.[546–548]

- Colistin or polymyxin B

Polymyxins, including colistin have potent *in vitro* activity against CRAB and are among the most studied antibiotics for systemic CRAB infections. Despite concerns about limited urinary concentrations, polymyxin B had equivalent success compared to colistin in multiple observational cohort studies of patients with MDR Gram-negative UTIs (including CRAB), with lower risks of nephrotoxicity.[525–528]

- Aminoglycosides

There is variable *in vitro* susceptibility among *Acinetobacter baumanii* isolates to aminoglycosides[545], but they are an attractive option for CRAB UTIs due to high renal excretion in their active form and potential for a single dose regimen.[230] Prior studies have shown good efficacy and minimal toxicity for aminoglycosides as treatment for UTIs due to a variety of multi-drug resistant pathogens, including some data that a single parenteral dose is effective for cystitis.[230,429–431,549]

- Minocycline, tigecycline, eravacycline, omadacycline

Both minocycline[543,550] and tigecycline[543,551,552] retain potent *in vitro* activity against CRAB and have been shown in case series to effectively treat CRAB UTI. No studies evaluating eravacycline use for CRAB UTI have been found during our investigation. While no clinical breakpoints for eravacycline currently exist for *Acinetobacter baumanii*, an epidemiologic study out of the SENTRY program found the MIC_{50} and MIC_{90} for over 2,000 *A. baumanii* (not all CRAB) isolates to be 0.5 mcg/mL and 1 mcg/mL, respectively.[553] Likewise, in a surveillance study from the SENTRY program, omadacycline was tested against 441 isolates of *A. baumanii* (not all CRAB) and the MIC_{50} and MIC_{90} for these isolates was determined to be 4 mcg/mL and 8 mcg/mL, respectively.[554] Like eravacycline, no clinical breakpoints currently exist for omadacycline for *Acinetobacter baumanii*. A small single center review of 19 *A. baumanii* isolates collected between 2004 and 2012 and found MICs for both eravacycline and omadacycline to be variable and dependent on the individual strain; the lack of clinical breakpoint interpretations and clinical outcomes limits the generalizability of the study.[555]

- Cefiderocol

Cefiderocol appears to have fairly reliable *in vitro* activity against CRAB[556], but clinical data for CRAB UTIs are lacking. In a phase 2 RCT (total n = 452, total CRAB isolates n = 1) of patients with MDR Gram-negative UTIs, outcomes were similar between patients receiving cefiderocol compared with imipenem/cilastatin treatment.[557] The CREDIBLE-CR trial was an RCT that examined cefiderocol compared with best available therapy for serious infections due to carbapenem-resistant Gram-negative bacteria (total n = 152, total CRAB isolates n = 54, total CRAB UTI = 1).[558] Overall, cefiderocol was found to have similar clinical and microbiological efficacy compared with best available treatment; due to small numbers, subgroup analyses with *A. baumanii* isolates were not available. Additionally, in 650 *Acinetobacter* spp isolates from 19 countries as part of the SENTRY surveillance

program found 97.7% of those isolates were susceptible to cefiderocol using the 2022 CLSI clinical breakpoint (MIC_{90} = 1 mcg/mL). The majority of isolates came from hospitalized patients with pneumonia.[559]

- Sulbactam/durlobactam

Sulbactam/dulobactam has only been FDA approved for the treatment of hospital or ventilator-acquired pneumonia and thus, the limited evidence available is exclusively in patients who meet those criteria.[532] No clinical data exist describing the use of sulbactam/durlobactam for the treatment of urinary tract infections, however the predominating route of elimination is renal with 75 to 85% of sulbactam and 78% of durlobactam being excreted in the urine unchanged.[560]

Antibiotic options for *S. maltophilia* are limited. Historically, trimethoprim/sulfamethoxazole and fluoroquinolones have been the most commonly prescribed antimicrobials for the treatment of UTIs due to *S. maltophilia*[529], perhaps on account of their demonstrated *in vitro* activity and clinical effectiveness in treating a variety of urinary tract infections. Notably, a retrospective observational study of 1,581 patients (identified between 2005 and 2017 via the Cerner HealthFacts database) with *S. maltophilia* infections received either levofloxacin (n = 823) or trimethoprim/sulfamethoxazole (n = 758) for treatment.[561] Overall, patients who received levofloxacin displayed similar mortality risk (adjusted OR = 0.76 [95% CI: 0.58 to 1.01]). Nearly all patients had respiratory tract infections (n = 1,452 or 91.8%) where levofloxacin was associated with a lower adjusted OR for death (0.73 [95% CI: 0.54 to 0.98]). As with all studies looking at *S. maltophilia,* it is challenging to distinguish true infection from colonization. In addition, treatment practices may have evolved over the period of 12 years in which the patients were recruited and polymicrobial cultures were included in the study. These key limitations dramatically restrict the external validity of the study. Our authors agree that there is equipoise for an RCT comparing levofloxacin to trimethoprim/sulfamethoxazole for *S. maltophilia* infections, including urinary tract infections.

Other options that have shown *in vitro* susceptibility and may be reasonable therapeutic alternatives include:

- Minocycline, tigecycline, eravacycline, omadacycline

Minocycline features good *in vitro* activity against *S. maltophilia*. A small single center retrospective study of 45 patients with primarily respiratory isolates and clinical syndromes did not find a difference in treatment failure between minocycline and trimethoprim/sulfamethoxazole.[562] Of note, only 3 patients in the minocycline group had a urine source while none in the TMP/SMX group had a urine source. Another small multicenter retrospective cohort study of 82 patients with *S. maltophilia* VAP found a lower clinical and microbiologic cure rate but no difference in 28-day mortality compared with fluoroquinolones.[552]

- Cefiderocol

Cefiderocol has been shown to have *in vitro* activity against *S. maltophilia*. An analysis of 338 *S. maltophilia* isolates from 19 countries as part of the SENTRY program showed 97.9%

susceptibility of cefiderocol based on the 2022 CLSI clinical breakpoints (MIC_{90} = 0.5 mcg/mL), though the vast majority of isolates came from hospitalized patients with pneumonia.[559] The APEKS-cUTI trial was published in 2018 and randomized patients to receive either cefiderocol or imipenem/cilastatin for complicated UTI treatment. Though very few of the isolates were *S. maltophilia*, outcomes were similar between patients receiving cefiderocol compared with imipenem/cilastatin.[557]

Treatment durations specifically for CRAB and *S. maltophilia* UTI have not been rigorously studied in clinical trials. Observational studies and RCTs published to date have reported variable durations of treatment ranging from 5 to 14 days.[121,122,557,563,564] There is currently no evidence to support the prolongation of therapy, beyond typical recommendations for treatment duration for urinary tract infections caused by CRAB or *S. maltophilia*. If a patient has clinically responded to empiric treatment for cystitis, but results of antimicrobial susceptibility testing reveal that the selected empiric agent is not active against the causative organism, we agree with the current consensus guidance that recommends against changing empiric therapy, extending treatment courses, or repeating urine cultures to document clearance.[219] If a patient with a systemic infection (e.g., febrile or bacteremic UTI, pyelonephritis, or BSI from a urinary source), most authors believe it to be most reasonable to change to an agent with demonstrated *in vitro* activity via AST and begin an evidence-based duration of therapy starting from the first date of active treatment.

Carbapenem-resistant Enterobacterales (CRE)

Carbapenem-resistant Enterobacterales (CRE) are defined as a member of the Enterobacterales and resistant to at least one carbapenem antibiotic and/or producing a carbapenemase enzyme.[565] The epidemiology of CRE is widely variable based on geographical location. For example, New Delhi metallo-β-lactamases (NDM) are common in Asia, OXA-48-type carbapenemases are common in Europe, and *Klebsiella pneumoniae* carbapenemases (KPC) are common in the United States, Latin America, and South America.[566–569] It should also be noted that mechanisms other than carbapenemase enzymes (such as porin mutations in OmpK36) may be responsible for carbapenem non-susceptibility in Enterobacterales.[569–571] The exact mechanisms of resistance (and thus optimal treatment) may be both relevant but also difficult to elucidate without advanced genomic testing such as whole genome sequencing.

For cystitis or CAUTI, oral nitrofurantoin is considered the preferred treatment option so long as the estimated creatinine clearance exceeds 30 mL/min[572–575] and the isolate shows *in vitro* susceptibility. As discussed in Sections 3 and 4, catheters should be exchanged or removed regardless of the time they have been in place if a patient is diagnosed with a CAUTI. When resistance or renal function preclude nitrofurantoin use, additional non-β-lactam options include:

- Trimethoprim/sulfamethoxazole
- Fosfomycin (for *E. coli*)
- Fluoroquinolones
- Single dose of an intramuscular or intravenous aminoglycoside

For patients with febrile or bacteremic UTI or pyelonephritis caused by CRE resistant to ertapenem but susceptible to meropenem (sometimes referred to as “mono-resistant CRE”), the

optimal treatment is unknown and the clinical implications of the discordant carbapenem susceptibilities are not well understood. Existing consensus guidance[219] offers extended infusion meropenem (or imipenem/cilastatin) as a potential option for treatment of mono-resistant CRE if a carbapenemase gene was not detected. We found minimal descriptive studies and no prospective studies to evaluate this approach.[576,577] For serious infections which are resistant to meropenem or imipenem, empiric treatment with ceftazidime/avibactam[506,578], meropenem/vaborbactam[579], imipenem/cilastatin/relebactam[508] are reasonable based on RCTs that demonstrated non-inferiority of these β-lactam combinations in the treatment of complicated UTIs. Of note, cefiderocol has two RCTs demonstrating non-inferiority to best available treatment[557,558], however there have been concerning trends published indicating higher than expected cefiderocol non-susceptibility rates amongst specific organisms.[580,581] Cefiderocol remains a reasonable option for severe infections due to CRE and there is no high quality data to suggest one of these agents is better than the other, but some authors would give consideration to the other BL/BLIs mentioned above before using cefiderocol. As discussed in the pyelonephritis section, aminoglycoside monotherapy is a reasonable alternative and may be of use for systemic infections from a urinary source infections in the setting of CRE.[429–431] Lastly, if a class B carbapenemase (metallo-β-lactamase) is detected, most authors consider aztreonam plus avibactam to be a reasonable empiric treatment option in order to spare patients the potential toxicities of other options, such as polymyxin-based combination treatment.[521,582,583]

There is currently no evidence to support the prolongation of therapy, beyond typical recommendations for treatment duration for urinary tract infections caused by CRE. If a patient has clinically responded to empiric treatment for cystitis, but results of antimicrobial susceptibility testing reveal that the selected empiric agent is not active against the causative organism, we agree with the current consensus guidance that recommends against changing empiric therapy, extending treatment courses, or repeating urine cultures to document clearance.[219] If a patient with a systemic infection (e.g., febrile or bacteremic UTI, pyelonephritis, or BSI from a urinary source), most authors believe it to be most reasonable to change to an agent with demonstrated *in vitro* activity via AST and begin an evidence-based duration of therapy starting from the first date of active treatment.

Enterobacterales with moderate to high risk of AmpC β-lactamase induction

Ambler class C (AmpC) β-lactamases hydrolyze penicillins, first through third generation cephalosporins, ceftaroline, and aztreonam. Cefepime, carbapenems, and non-β-lactam agents are generally capable of withstanding hydrolysis by Amp-C β-lactamases.[584] While many Enterobacterales have chromosomally-encoded *ampC* genes, they may (like *E. coli*) lack the inducible mechanisms that lead to high levels of AmpC production that may impact clinical outcomes.[585,586] Enterobacterales also vary widely in the extent of AmpC expression at basal and induced levels. Antibiotics such as amoxicillin, first generation cephalosporins, and cephamycins are potent inducers of AmpC production, whereas piperacillin/tazobactam and third generation cephalosporins are less potent, but can still induce increased production. The totality of evidence suggests that three organisms (*Enterobacter cloacae, Klebsiella aerogenes, and Citrobacter freundii*) have some of the highest basal levels of AmpC production and achieve the highest AmpC enzyme levels when induced, thus have the highest risk for impacting MICs and patient outcomes. Small studies indicate that hyperproduction of AmpC (thus, initial

susceptibility to drugs like ceftriaxone followed by the development of resistance) can happen in up to about 20% of isolates.[586–594] This change from initial susceptibility to resistance has been shown to occur as soon as 1 day after initiation of an AmpC production inducer[595]. Other organisms commonly included in various mnemonics (e.g., SPACE, SPICE) to help remember AmpC producers such as *Serratia marcescens, Morganella morganii*, *Providencia* spp. appear to only hyperproduce AmpC to a clinically significant level less than 5% of the time.[591,596] Newer mnemonics (e.g., HECK-Yes) were created to include less common bacteria capable of clinically significant AmpC hyperproduction, such as *Hafnia alvei* and *Yersinia enterocolitica*, however data is limited with regard to both descriptive and interventional studies.[597–600]

For cystitis or CAUTI, oral nitrofurantoin is considered the preferred treatment option so long as the estimated creatinine clearance exceeds 30 mL/min[572–575] and the isolate shows *in vitro* susceptibility. As discussed in Sections 3 and 4, catheters should be exchanged or removed regardless of the time they have been in place if a patient is diagnosed with a CAUTI. When resistance or renal function preclude nitrofurantoin use, additional non-β-lactam options include:

- Trimethoprim/sulfamethoxazole
- Fluoroquinolones
- Single dose of an intramuscular or intravenous aminoglycoside

For patients with febrile or bacteremic UTI, pyelonephritis caused by an AmpC-producing Enterobacterales, empiric treatment with cefepime or a carbapenem is reasonable based on its weak propensity to induce AmpC production and stability even in the presence of AmpC hyperproduction until AST results are available.[601,602] As previously mentioned, when certain organisms with a lower propensity to hyperproduce AmpC to a clinical significant level (e.g., *Morganella morganii*) are identified, some clinicians and stewards may advocate for the use of ceftriaxone, even in the setting of severe infections.[603,604] Once available, the ideal definitive treatment option will depend on compelling indications, patient-specific contraindications, and/or *in vitro* susceptibility. Of note, organisms displaying elevated MICs to cefepime (e.g., 4 mcg/mL or higher) may elevate suspicion for concomitant ESBL-production and a carbapenem or transition to a non-β-lactam antimicrobial should be considered.[219,605,606] Tazobactam poorly protects piperacillin from hydrolysis by AmpC organisms resulting in potential treatment failures, thus based on observational evidence, the authors prefer using cefepime or carbapenems in serious infections due to AmpC-producting Enterobacterales.[607–610] It should be noted that once the transition to oral antimicrobials occur, trimethoprim/sulfamethoxazole and fluoroquinolones remain preferred options. Oral cephalosporins, for example, are unlikely to achieve high enough levels to overcome basal or elevated levels of AmpC production.

There is currently no evidence to support the prolongation of therapy, beyond typical recommendations for treatment duration for urinary tract infections caused by AmpC-producing Enterobacterales. If a patient has clinically responded to empiric treatment for cystitis, but results of antimicrobial susceptibility testing reveal that the selected empiric agent is not active against the causative organism, we agree with the current consensus guidance that recommends against changing empiric therapy, extending treatment courses, or repeating urine cultures to document clearance.[219] If a patient with a systemic infection (e.g., febrile or bacteremic UTI, pyelonephritis, or BSI from a urinary source), most authors believe it to be most reasonable to

change to an agent with demonstrated *in vitro* activity via AST and begin an evidence-based duration of therapy starting from the first date of active treatment.

Extended spectrum beta lactamase-producing Enterobacterales (ESBL-E)

Extended spectrum β-lactamases (ESBLs) hydrolyze penicillins, first and third generation cephalosporins, cefepime, ceftaroline, and aztreonam.[584] Although any gram-negative organism may carry ESBL genes, *Proteus mirabilis, Escherichia coli, Klebsiella pneumoniae,* and *Klebsiella oxytoca* are the organisms most commonly associated with ESBL production.[602,611] While CTX-M-15 has become the most commonly identified gene associated with ESBL producing clinical isolates, there are over 150 distinct ESBL enzymes that have been found.[612]

Although organisms expressing a gene resulting in ESBL production commonly also carry other resistance determinants that can result in resistance to other classes of antimicrobials[613–616], non-β-lactam antimicrobials (as they are not cleaved by ESBL enzymes), are appealing choices for the treatment of urinary tract infections due to ESBL-E. For cystitis or CAUTI, oral nitrofurantoin is considered the preferred treatment option so long as the estimated creatinine clearance exceeds 30 mL/min[572–575] and the isolate shows *in vitro* susceptibility. As discussed in Sections 3 and 4, catheters should be exchanged or removed regardless of the time they have been in place if a patient is diagnosed with a CAUTI. When resistance or renal function preclude nitrofurantoin use, additional oral non-β-lactam options include:

- Trimethoprim/sulfamethoxazole
- Fosfomycin
- Fluoroquinolones

If AST reveals no oral options, the following treatment options are reasonable:

- Single dose of an intramuscular or intravenous aminoglycoside
- Carbapenems

For patients with febrile or bacteremic UTI or pyelonephritis caused by an ESBL-producing Enterobacterales, empiric treatment with a carbapenem is reasonable until AST results are available.[606,617] Once available, the ideal definitive treatment option will depend on compelling indications, patient-specific contraindications, and/or *in vitro* susceptibility.

There is currently no evidence to support the prolongation of therapy, beyond typical recommendations for treatment duration for urinary tract infections caused by ESBL-producing Enterobacterales. If a patient has clinically responded to empiric treatment for cystitis, but results of antimicrobial susceptibility testing reveal that the selected empiric agent is not active against the causative organism, we agree with the current consensus guidance that recommends against changing empiric therapy, extending treatment courses, or repeating urine cultures to document clearance.[219] If a patient with a systemic infection (e.g., febrile or bacteremic UTI, pyelonephritis, or BSI from a urinary source), most authors believe it to be most reasonable to change to an agent with demonstrated *in vitro* activity via AST and begin an evidence-based duration of therapy starting from the first date of active treatment.

Methicillin-resistant Staphylococcus aureus (MRSA)

Staphylococcus aureus may be categorized as methicillin-susceptible or methicillin-resistant. The latter is most frequently associated with the detection of the *mecA* gene.[618] This gene encodes for a low-affinity penicillin-binding protein, PBP2a and confers resistance to most β-lactams except for ceftaroline and ceftobiprole.[619,620]

Staphylococcus aureus is an uncommon cause of urinary tract infections in the general population and the most commonly cited risk factor is urinary tract catheterization or instrumentation.[621] A classical teaching is that when *S. aureus* is cultured from the urine it may be reflective of a "descending" infectious process where bacteremia seeds the renal collecting system, rather than an isolated urinary infection and warrant additional work-up for invasive infection with blood cultures.[622] However, it is important to make the distinction between prevalent *S. aureus* bacteriuria (SABU) in patients with *S.* aureus bacteremia (SAB) and the incident SAB in patients with SABU. Among patients who develop SAB, the prevalence of SABU has been reported to be 8 to 39% and is a poor prognostic sign associated with increased mortality.[621] Conversely, the incidence of SAB in patients with SABU is less than 7% and based on study design, this may be an overestimate.[621,623,624] Avoidance of unnecessary blood cultures is prudent since they can result in numerous economic and clinical ramifications.[625] The authors favor treatment of patients with SABU and urinary symptoms, otherwise treatment of ASB due to *S. aureus* or routine blood cultures do not seem warranted unless there are clinical signs or symptoms of infection, or the patient has another indication for the treatment of ASB (reviewed in question 24). If invasive infection is present, the duration of therapy of the invasive process should supersede that of a urinary tract infection; for example, with MRSA infective endocarditis.[626] When invasive infection can be ruled out, there are limited clinical data to suggest that the presence of antimicrobial resistance should prompt a duration of therapy beyond what is recommended for each classification of urinary tract infection. Treatment options for urinary tract infections caused by *Staphylococcus aureus* vary depending on susceptibility results, but may include vancomycin, daptomycin, trimethoprim/sulfamethoxazole, or linezolid.

Ampicillin-resistant and/or vancomycin-resistant Enterococci

Antimicrobial resistance associated with Enterococci vary based on agents used and species of Enterococci evaluated. Resistance to penicillins is associated with penicillin binding protein (PBP) gene expression and mutations and may be expressed by any enterococci, though E. faecium expresses these genes more frequently than other species. Another class of antimicrobials with enterococcal coverage includes glycopeptides (vancomycin and teicoplanin). Resistance to glycopeptides have been associated with the presence of vancomycin resistance gene clusters (van). *vanA* and *vanB* are the most common clusters associated with glycopeptide resistance. Again, these are commonly found in E. faecium isolates, but clinicians should be aware that *E. gallinarum* and *E. casseliflavus* intrinsically carry vanC conferring low-level resistance to glycopeptides.[627]

Urinary tract infections caused by *Enterococcus* spp. are primarily nosocomial in nature, and represent a smaller proportion of community-acquired infections. As such, presence of indwelling catheters and other complicating factors should be considered carefully when selecting a duration of antimicrobial therapy. There is a paucity of evidence to suggest that

urinary tract infections caused by resistant *Enterococcus* spp. require longer durations of therapy compared to infections caused by non-resistant organisms. Therefore, clinicians may consider treatment durations that conform to the recommended durations for the classification of urinary tract infection (e.g., cystitis or pyelonephritis) caused by non-resistant organisms.
Due to high urinary penetration, aminopenicillins have demonstrated clinical success in observational studies in patients with urinary tract infections caused by ampicillin-resistant, and/or vancomycin-resistant *Enterococcus* spp. and are reviewed in table 24.[628–631] Other potential treatment options may include daptomycin, nitrofurantoin, fosfomycin (for *E. faecalis*), levofloxacin, or linezolid.[632–634]

Table 24. Outcomes of observational studies comparing the use of aminopenicillins vs. other antibiotics for cystitis due to ampicillin or vancomycin-resistant *Enterococcus* spp.

Study	Comparator(s)	Population	Outcome(s)
Richey et al.[628](2015)	Amoxicillin vs. nitrofurantoin	Ampicillin-resistant *E. faecium* UTI	Clinical cure: 100% (AMOX) vs. 77% (NTF), p = 0.47
Cole et al.[629](2015)	Aminopenicillins vs. non-β lactam	Symptomatic UTI due to vancomycin-resistant Enterococci (35% of VRE isolates were susceptible to ampicillin)	Clinical cure: 83.9% (aminoPCN) vs. 73.3% (non-β lactam), p = 0.32 30-day retreatment: 12.9% (aminoPCN) vs. 13.3% (non-β lactam), p = 0.96
Shah et al.[630](2018)	Aminopenicillins (descriptive study)	Symptomatic UTI due to ampicillin and vancomycin-resistant Enterococci	Clinical cure: 74 of 84 (88.1%) Microbiological cure: 50 of 58 (86%)
Montes de Oca et al.[631](2023)	Aminopenicillins vs. other antibiotics	Symptomatic UTI due to Enterococci	Clinical success at 14 days: 83.1% (aminoPCN) vs. 82% (non-aminoPCN); RD = 1.1% (97.5% CI: -0.117 to 0.139)

Q27: What are effective antimicrobial stewardship strategies that can optimize the rational and sustainable use of antimicrobials in the setting of treatment of urinary tract infections?

Clear Recommendation for de-escalation and oral treatment

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation) for allergy assessment and cascade reporting

Executive summary

Randomized controlled trials have demonstrated the individual and ecological benefits to antibiotic de-escalation and all authors encourage its use when able during the treatment of urinary tract infections. [635,636] Additionally, multiple RCTs demonstrate oral treatment of a variety of UTIs with all or mostly oral regimens result in comparable outcomes to intravenous-only treatment and may reduce hospital length of stay and adverse events related to antibiotics and/or central venous catheters.[637–650] Our review did not yield any RCTs evaluating antibiotic allergy assessment specifically for the management of UTIs, however all authors agree that thorough allergy assessment (and challenge, if indicated) can likely prevent a variety of harms based on existing data and recommendations from specialists in allergy/immunology.[651–653] Although we cannot provide a clear recommendation due to the observational nature of the data, all authors agree that optimizing the reporting of antimicrobial susceptibility results through selective or cascade reporting is a reasonable strategy to optimize treatment selection.[265,654,655]

Overall summary

Antibiotic de-escalation

Antimicrobial de-escalation (ADE) is the practice of discontinuing antibiotics or narrowing antimicrobial spectrum to more directly target identified organisms causing an infection. For patients with urinary tract infections, including more severe infections and those involving bacteremia, de-escalation can be rationally done based on the identification of specific organisms and *in vitro* susceptibility in culture from blood, urine, or abscess fluid. Clinical context (e.g., hemodynamic stability, fever trend, etc.) is an important component to assessing if de-escalation is warranted at any given point in time. Two randomized trials have been published comparing clinical outcomes of patients with suspected or confirmed sepsis (13-22% of cases attributed to a urinary source), who underwent de-escalation or discontinuation compared to continued, empiric therapy and found no difference in mortality among groups.[635,636] Multiple observational studies and systematic reviews have also found that the practice of ADE is safe for patients, without increasing harm due to undertreatment.[656–659]

Regarding antibiotic discontinuation as a cornerstone of ADE, a meta-analysis of three randomized, controlled trials among patients with bacteremia (55-68% originating from urinary sources), evaluated outcomes of shorter antibiotic durations compared to standard courses. Findings demonstrated no increase in mortality, infection relapse or complication, length of hospitalization, nor rate of adverse events when compared to longer antibiotic durations.[440] Similarly, observational data among 1,099 patients with bacteremic urinary infections across 24 US hospitals demonstrated that dose-optimized, targeted antibiotics used for 7-day durations resulted in similar outcomes including mortality and infection recurrence compared to longer therapies (adjusted OR = 0.76 [95% CI: 0.38 to 1.52]).[563] Evidence also supports use of ADE and shorter duration in more severe urinary infections (e.g., pyelonephritis, bacteremia secondary to urinary source), which encourages enhanced consideration for ADE and optimized antibiotic exposure (e.g., tailored spectrum, effectively shorter durations) for less severe urinary infections (e.g., cystitis, catheter-associated UTI). In these situations, the authors believe that oral antibiotic therapy utilizing pathogen-directed, narrow-spectrum agents is often optimal.

ADE is a crucial component in the fight against antimicrobial resistance as numerous population-based studies of antibiotic use in both humans and agriculture have found that reduced antibiotic exposure is associated with diminished selective pressure and subsequent resistance at the population level.[660–673] Since all antibiotics may contribute to adverse events, targeted antibiotics for the shortest effective duration may promote safety to limit untoward effects, including risk of resistance development. Given the accumulated evidence of safety from systematic literature reviews of ADE and shorter durations, it is rational and preferred to incorporate these practices when using antibiotics for UTI treatment to promote optimal outcomes and minimize harm to the patient and society.

All or mostly oral treatment regimens.

While it is well-established and rational that oral regimens are preferred and routinely utilized for treatment of cystitis, mounting evidence supports routine consideration of empiric or definitive (transition) oral regimens for more severe urinary infections, including pyelonephritis and UTI complicated by bacteremia (see questions 22 and 24). Unfortunately, observational data indicate the adoption of all or mostly oral treatment regimens is lower than it should be.[674] More than 20 concordant randomized trials have shown that treatment with oral antimicrobials are at least as effective as intravenous-only treatment, even for deep-seated and complex infections such as bloodstream infections, infective endocarditis, and various bone and joint infections.[675] The benefits of oral antimicrobial treatment should be viewed in the context of comparable (or improved) patient outcomes while avoiding iatrogenic harms, such as complications related to central venous catheter use[637–640,676,677], hospital length of stay[644–650,678,679], overall healthcare costs[680,681], and antimicrobial-related side effects.[641–643,682] In the interest of beneficence and the presented compelling evidence, all authors encourage consideration of all oral regimens or early transition from IV to oral therapy in patients with UTI when they are clinically stable, able to take oral medications with no absorption concerns, and have achieved source control when applicable. Additionally, the authors prefer the use of the term “oral transition” as opposed to “oral stepdown” as the term “stepdown” may insinuate that oral treatment is less effective than parenteral treatment.

Antibiotic allergy assessment and challenge.

Antibiotic allergy labels are associated with increased length of hospital stay, readmission rates, development of multi-drug resistant organisms, healthcare related costs, and antibiotic treatment related adverse effects such as *C. difficile* infection.[683] UTIs are consistently identified within the top five most frequent indications for antimicrobial prescribing.[684,685] The volume of antibiotics prescribed for UTIs and predisposition many patients have for recurrent and eventually multidrug resistant UTIs[686] highlights the importance of optimizing treatment options early on. Our review did not identify any studies evaluating the impact of antibiotic allergy evaluation specifically for management of UTIs. However, thorough allergy assessment and challenge when appropriate is recommended to optimize antimicrobial selection when treating any type of infection.[687] Although no studies have evaluated the management of β-lactam or sulfonamide allergy in the context of UTI, the potential benefits of this may be extrapolated from that of other disease states and through official guidance provided by the American Academy of Asthma, Allergy, and Immunology (AAAAI).[651] The ability to perform

simpler allergy assessments and challenges has led health systems to take a proactive approach to allergy de-labeling. All authors encourage careful and intentional assessment of the patients allergies as to avoid the detrimental harms associated with antibiotic allergy labels and as an overall cost savings initiative.[653,688,689]

β-lactam allergies are most common antibiotic allergy labels and reported by approximately 10-15% of the population.[652,690,691] Various studies have suggested that patients with a documented penicillin allergy are more likely to receive alternative, non-β-lactam agents than those without such an allergy label and this association appears to be stronger amongst patients receiving treatment for UTI than other common infections.[692] As alluded to above, antibiotic allergies have been associated with iatrogenic harms and this is especially true for those with penicillin allergies.[652,693] For patients who describe an expected antimicrobial side effect (e.g., nausea, vomiting, diarrhea) or a reaction inconsistent with true allergy (e.g., family history of penicillin allergy or headache), those can reasonably be de-labeled without any challenge or skin testing.

Sulfonamide allergies are the second most reported antibiotic allergy, reported by approximately 5-10% of the population.[652,690,691] Many factors should be considered when evaluating whether trimethoprim/sulfamethoxazole could be a treatment option for a patient with a sulfa allergy label. First, many commonly used non-antibiotic medications feature a sulfa moiety (e.g., loop and thiazide-type diuretics, sulfonylureas, tamsulosin, celecoxib, etc.) but do not cross-react with sulfonamide antibiotics, so it is important to delineate between the two when assessing a patient's allergy history.[694] The approach to sulfonamide allergies has evolved significantly over time. Instead of recommending time and resource-intensive desensitization protocols, direct oral challenges have become the new standard with rates of tolerance comparable to traditional desensitization being demonstrated in available prospective studies.[651,695,696] This has been adopted as the preferred approach amongst patients with a history of a benign cutaneous reaction (such as urticaria or morbilliform drug eruption) that occurred over 5 years ago according to the AAAAI, including patients living with HIV.[651,697] For reactions that occurred within the last 5 years, the AAAAI suggests a 2-step challenge, including patients living with HIV.[651] However, it is important to keep in mind that sulfonamide hypersensitivity reactions can be delayed T-cell mediated reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or Stephens Johnson syndrome (SJS). These types of reactions are strict contraindications to re-exposure to the offending agent.[651,698]

Antimicrobial susceptibility testing reporting.

Antimicrobial susceptibility testing is routinely employed to optimize management of many infectious disease states. It has been well documented that antimicrobial resistance (AMR) has increased in recent years including contributing to higher rates of hospitalization due to urinary tract infections.[699] In addition to identifying resistant isolates, antimicrobial susceptibility testing may be used to optimize patient care through antimicrobial selection and dose optimization. However, indiscriminate reporting of antibiotic susceptibility for certain organisms in the urine may lead to overutilization of antimicrobials. Additionally, several observational studies have evaluated the use of antibiotics in UTIs caused by pathogens conveying genotypic or phenotypic resistance to the selected antimicrobial with no differences in rates of either clinical cure or microbiological eradication. Pathogen/antibiotic combinations evaluated in these

studies include aminopenicillins for ampicillin- and vancomycin-resistant *Enterococcus* spp.[628–631] and cefepime or piperacillin/tazobactam for ESBL-producing Enterobacterales.[700–705]

Antimicrobial susceptibility breakpoints are based on a variety of sources including in vitro data, pharmacokinetic and pharmacodynamic properties, and clinical trials. Notably, many antimicrobial susceptibility breakpoints are based on pathogens isolated from the blood. Of note, some pathogen/antibiotic susceptibility breakpoints are targeted towards urinary isolates, namely fosfomycin, nitrofurantoin, and aminoglycosides for the treatment of *Pseudomonas aeruginosa.* Others are used as surrogates for other medications such as cefazolin for oral cephalosporins including cefdinir, cefpodoxime, and cefuroxime.[706] Given the difficulty in establishing universal breakpoints, relatively lower inoculum of bacteria associated with UTIs, and often higher than serum levels of antimicrobials achieved in the urine, providers should consider medication-specific pharmacokinetic and pharmacodynamics factors such as urinary penetration, bioavailability, and wild-type distribution MICs when interpreting and applying clinical breakpoints and minimum inhibitory concentrations to patient care.

Cascade reporting of urine culture antimicrobial susceptibility results is a strategy to promote the utilization of the most effective antimicrobials with lowest risk for collateral damage.[687] Specific examples include suppressing the results of: antimicrobials that may demonstrate a low degree of urinary penetration and therefore be suboptimum treatment when alternatives exist (e.g., tetracyclines); or antimicrobials that may be effective for UTI but have a high degree of collateral damage making alternative agents preferred (e.g., fluoroquinolones). Impact of cascade reporting on treatment of UTIs has never been evaluated in a controlled study. Retrospective studies have sought to evaluate the impact of cascade reporting on prescribing habits for UTIs and have demonstrated successful results.

In a single center quasi-experimental study, the impact of a cascade reporting intervention on the defined daily doses (DDD) per 1,000 patient days of ciprofloxacin across all indications was evaluated.[655] Prior to the intervention, ciprofloxacin susceptibility results were reported for all Enterobacterales regardless of susceptibility to other agents. The intervention involved suppressing ciprofloxacin susceptibility to Enterobacterales, for all sites of infection (though UTI was the most commonly reported source), when susceptibility was demonstrated to all other agent on the Gram-negative panel. The mean monthly ciprofloxacin DDD per 1,000 patient days dropped from 87 (95% CI, 83.7 to 91.2) to 39 (95% CI, 35.0 to 44.0) after the intervention. In a large retrospective cohort study including 113,780 urine cultures positive with *Escherichia coli*, *Klebsiella* spp., or *Proteus mirabilis*, the investigators evaluated whether laboratory variation in selective reporting influenced prescribing decisions for outpatient UTIs.[265] Certain antimicrobials were reported in the vast majority (>95%) of laboratory reports: nitrofurantoin, trimethoprim/sulfamethoxazole, ciprofloxacin, and cephalexin, while certain antibiotics were reported less frequently: amoxicillin/clavulanate (27.6%) and third generation cephalosporins (30.1%). Reporting of antibiotic susceptibility was associated with nearly three-fold increased prescribing of antibiotics with the result reported (adjusted OR = 2.98 [95% CI: 2.07 to 4.28]). In a single center quasi-experimental study including 209 hospitalized patients, antibiotic discharge prescribing for UTIs was evaluated before and after implementation of a cascade reporting intervention, which suppressed fluoroquinolone susceptibility results for pan-susceptible *Escherichia coli* or *Klebsiella* spp.[654] There was a significant reduction in

fluoroquinolone prescribing at discharge (adjusted RR = 0.61 [95% CI: 0.4 to 0.93]). Clinical outcomes of the intervention were not evaluated.

eAppendix 5: SPECIAL POPULATIONS & GENITOURINARY SYNDROMES

Q28: What are special considerations for the diagnosis and treatment of urinary tract infections in older adults?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive summary

Asymptomatic bacteriuria is prevalent in older adults, particularly in institutionalized individuals, with treatment showing no benefit over placebo.[[707,708]] Over-testing and overtreatment with antibiotics for these non-symptomatic cases remains high.[709,710] UTIs are more frequent in the institutionalized older adults and clinical tools for assessing symptoms exist to help discourage tests for non-delirium behavioral changes or falls.[709] Utilizing clinical scores alongside microbiological tests is crucial due to the high rates of bacteriuria with pyuria, and the potential misinterpretation of UA results, which often leads to unnecessary antibiotic use.[711,712]] Further research comparing clinical prediction scores for UTIs is needed.

Overall summary

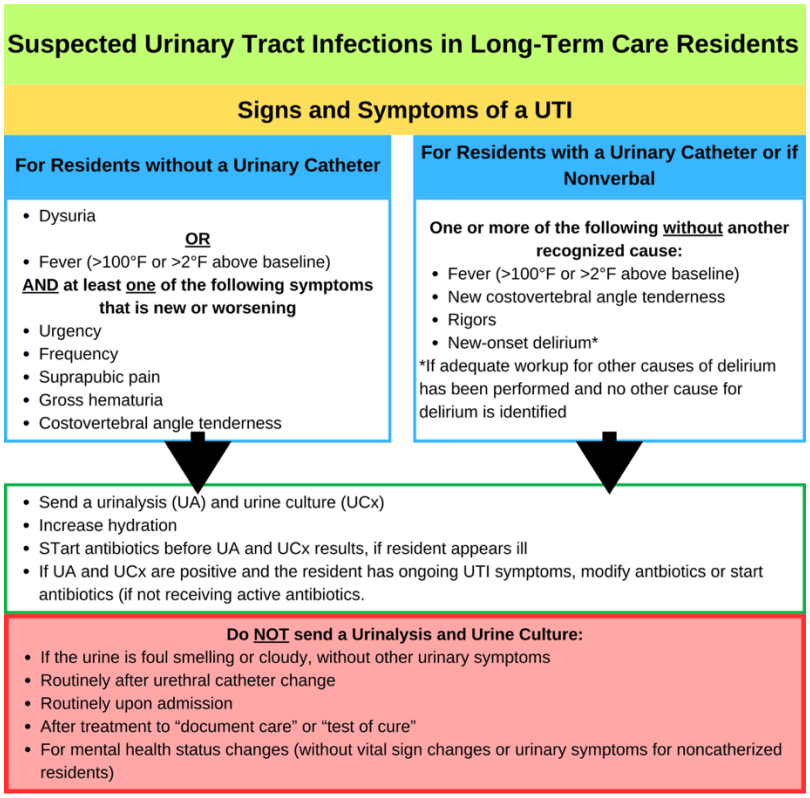
Clinical Evaluation

ASB is more common in older adults compared to other groups.[[713]] While rates range only 1-5% in healthy populations, these rates are double to triple that in healthy individuals, and up to 15-50% in institutionalized older adults.[[457,707]] A meta-analysis of six RCTs embedded within the European Association for Urology guidelines on urological infections (n = 328 older adults) shows no benefit over placebo for antimicrobial treatment of ASB.[[108]] Despite this consensus, rates for inappropriate antibiotic prescriptions for ASB range over 35% in institutionalized older adults.[[714]]

UTIs are more common in the institutionalized older adults and the optimal threshold for UTI testing and diagnosis in institutionalized older adults is challenging to determine. The Society of Healthcare Epidemiology of America (SHEA) convened an expert panel to help delineate management in this subject, recommending a systemized clinical tool to assess for delirium such as the “confusion assessment method” or the updated McGeer criteria.[[715,716]] The consensus group does not recommend UTI testing for falls alone, or for behavioral changes that do not formally constitute delirium. In addition, multiple metrics from the US Agency for Healthcare Research and Quality [[717]] and the validated Loeb Minimum Criteria [[718]] outline clinical criteria for a more standardized approach for UTI testing in nursing home residents. Notably, these criteria do not include symptoms of abnormal urine odor or color, which is commonly misinterpreted by patients and families as possible symptoms of UTI.[[719]] A Delphi consensus among international experts led to the development of a decision tool for empiric antibiotic

treatment of suspected UTIs in frail older adults, emphasizing the evaluation of nonspecific symptoms for other causes and limiting treatment decisions based on urinalysis unless both nitrite and leukocyte esterase are negative.[720]

Figure 8. Proposed assessment framework for patients with suspected urinary tract infection who live in long-term care facilities.



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It is especially important to consider clinical scores such as these in conjunction with microbiological testing, as both UA and urine culture in older adults are quite difficult to interpret otherwise. In addition to the high ASB rates, over 90% of cases with bacteriuria also have associated pyuria.[721] While the negative predictive value of UA dipstick testing is strong in nursing home residents, the positive predictive value is poor, with a specificity approaching only 20%.[716,722] However, the sensitivity is contingent on the cut-off values and urinalysis methods used. Adjustments, such as employing higher cutoffs for pyuria, may prove beneficial in specific clinical scenarios. Microbiologic testing should not be obtained without proper pretest probability of infection gleaned through validated clinical scoring systems, as data suggests that positive UA and/or urine culture will ultimately lead to antibiotic prescriptions in this population, especially in institutionalized settings without strong stewardship systems of provider education.[716,723] Further randomized trials might consider comparison of available clinical prediction scores for UTI.

Treatment Approach

A Cochrane review of 15 randomized controlled trials (total n = 1,644) evaluated duration of treatment for uncomplicated UTI in older adult women.[288] This evaluation found that treatment efficacy did not differ between "short-course" (3-6 days) compared to "long-course" (7-14 days) of antibiotics among older adult women with uncomplicated cystitis. Three studies compared single-dose to short-course. Six studies compared single-dose to long-course. Six studies compared short-course to long-course. Within 2 weeks post-treatment, there was a significant difference for persistent UTI between single-dose and short-course treatment (RR = 2.01 [95% CI: 1.05 to 3.84]) and single versus long-course treatment (RR = 1.93 [95% CI: 1.01 to 3.70]). No differences in long-term persistent UTI, clinical failure or reinfection rates were observed between single-dose versus short-course or single-dose versus long-course or short-course versus long-course. One study found that patients preferred single-dose treatment (RR = 0.73 [95% CI: 0.60 to 0.88]) compared to long-course treatments. Overall, the findings support short course (3-6 days) but not single dose (except for when using an aminoglycoside [230]) for the treatment of cystitis in older adult women.

Overall conclusion

Over-treatment of ASB in older adults remains common. Clinical tools such risk scores, best practice alerts, diagnostic stewardship and antimicrobial stewardship can be used to avoid unnecessary testing and treatment. More research on clinical prediction scores for UTIs is needed.

Q29: What is the role and utility of urinalysis and urine culture testing in pediatric populations?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

In pediatric care, the workup for febrile illness often includes UA and urine culture, particularly in younger populations where symptoms cannot be elicited.[724] These practices can lead to the overtreatment and overdiagnosis of UTI. Major societies recommend using proper microbiological methods for diagnosis, yet real-world practices deviate, relying on less reliable methods like bagged urine samples.[725–727] The interpretation of UA and colony forming unit counts in urine cultures in the pediatric population are not clearly defined, leading to variability in the diagnosis and treatment of pediatric UTI.

Overall summary

UA and urine culture are frequent components of workup for pediatric febrile illness, both in primary care[6] as well as acute-care encounters including emergency room visits and hospitalizations.[728] While UTI is highly prevalent in general pediatrics, evidence suggests that UTI is also overtreated [729] and over-diagnosed[724] in many pediatric settings. In particular, the pediatric urgent care and emergency care literature[730–732] shows much evidence of inappropriate diagnostic and prescribing practices and "real-world" deviation from societal guidelines.

Diagnosis is often based on bagged urine samples [733,734] or diaper cultures [735], despite substantial evidence suggesting poor sensitivity and specificity. Empiric antibiotic prescriptions often occur without appropriate microbiological findings or sometimes based on incidental microbiologic findings without symptoms. In addition, early discontinuation of antibiotics on basis of follow up urine cultures often occurs less frequently than desired.[731,732,736,737]

The American Academy of Pediatrics and other international societies recommend that a UA be performed with urine culture to formally diagnose UTI in medical settings.[6,726,737] However, there is still controversy regarding proper interpretation of UA and urine culture in combination. Proprietary statistical calculators have been developed in experimental settings to risk stratify patients with possible UTI (e.g., to increase pre-test probability) [738], but none have established uniform approval. There is no consensus across international guidelines for the number of "colony forming units" (CFU) per milliliter on urine culture that is diagnostic of UTI[726,733], especially in neonatal patients.[739] Evidence has suggested that true UTIs can still occur in children with CFU at counts less than the traditionally accepted 10^5 CFU per mL. In addition, variable interpretation of UA and urine cultures is seen in certain subpopulations.[733] Evidence also suggests that isolated UA abnormalities such as dipstick nitrite results[733,740] and microscopic urine WBCs at varied specific gravities [741,742] may show limited sensitivity in infants and young children. Similar variable accuracy of these findings can occur in children with baseline common, benign genitourinary abnormalities such as childhood vulvovaginitis and phimosis [743], febrile neutropenic patients [744], and patients with UTI not due to *Escherichia coli*.[725,745,746]

Overall conclusion

In pediatric care, UA and urine cultures are frequently used for febrile illnesses, often leading to overdiagnosis and overtreatment of UTIs. UA and urine cultures should be ordered in the proper setting and clinical judgement used to interpret their results.

Q30: For pediatric patients, how do we delineate cystitis vs. pyelonephritis when the child is unable to verbalize symptoms characteristic of urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Pediatric cystitis and pyelonephritis are common yet complex conditions in children, impacting quality of life and requiring comprehensive management.[747,748] In pediatric patients, distinguishing cystitis from pyelonephritis can be challenging, particularly in young children who are unable to verbalize symptoms. Clinical evaluation, including assessment for systemic signs such as fever and poor feeding, along with urinalysis and imaging studies, are essential in making this differentiation.[18,218] While infections are mainly caused by gram-negative bacteria, non-infectious causes also contribute to the diagnostic challenge. Prevention of long-term renal damage from pyelonephritis necessitates prompt recognition and treatment, considering genetic, urinary, and environmental factors.

Overall summary

Pediatric cystitis, an inflammation of the urinary bladder in children, is a frequently overlooked yet prevalent medical condition that significantly impacts a child's quality of life.[747] Despite often being overshadowed by other urological disorders, such as vesicoureteral reflux or obstructive uropathies, cystitis in children is a considerable concern. Its manifestations can vary across all age groups, with infection-related cystitis, mainly caused by gram-negative bacterial pathogens (especially *Escherichia coli*), remaining predominant.[749] Non-infectious forms including radiation-induced or interstitial cystitis, though less common, add to diagnostic complexity.[750] Evidence suggests a multifactorial etiology involving genetic predisposition, urinary dysfunction, and environmental factors, with traditional subtypes including uncomplicated as well as complicated cystitis in the setting of patient comorbidities.

Similarly, pediatric pyelonephritis, characterized by kidney infection and inflammation, poses a significant clinical challenge in pediatric urology and nephrology. Despite being common, it is often underappreciated in complexity and clinical implications, requiring vigilant recognition and management to prevent potential long-term renal consequences in children.[748] Pyelonephritis typically results from ascending gram-negative UTIs, and its course is influenced by a complex interplay of host factors, microbial virulence, and anatomical peculiarities of the urinary tract.

Traditionally, pyelonephritis has been considered difficult to distinguish between cystitis on clinical grounds alone in patients under two years old.[751] Traditional symptoms of UTI are considered easier to verbalize among children older than five years of age[752], but there are still substantial numbers of children who subjectively experience atypical clinical symptoms of both cystitis as well as pyelonephritis. In addition, young infants are considered particularly high risk for complications from this disorder, especially if there is concern for infantile sepsis syndrome.

This contributes to guideline-based recommendations for hospitalization in patients with any nonsubtyped UTI if they are under two months of age.[218] However, retrospective analysis suggests that there is significant practice variation across institutions regarding which infants are ultimately determined to require hospitalization.[753] Additionally, more recent retrospective health outcome data[753,754] and econometric data[755] suggests potential benefit for early discharge in young infants with low clinical risk for bacteremia. Multicenter controlled trials are needed to develop a more robust evidence base for hospitalization.

Overall conclusion

Pediatric cystitis and pyelonephritis are common. Prompt diagnosis and empiric therapy is key to preventing long-term renal damage from pyelonephritis, taking into account genetic, urinary, and environmental factors.

Q31: What is the optimal follow up timeframe for pediatric patients with urinary tract infections?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Observational data suggests that clinical improvement including fever resolution typically occurs after 48 to 72 hours of treatment in children. Authors believe it to be reasonable to conduct additional work-up (e.g., renal and bladder ultrasonography) and/or reassess the current treatment plan if patients do not experience clinical improvement within that timeframe. Assuming the patient improves as expected, previously described treatment durations of 3 to 5 days for cystitis and 7 to 10 days for pyelonephritis are reasonable (more detail in questions 19 and 20). Routine follow-up is not necessary unless the patient is younger than 2 years old and experiences a febrile UTI or a child of any age experiences a recurrence of febrile UTI. It is reasonable to de-escalate and/or target treatment as soon as culture and susceptibility results are available.

Overall summary

Based on observational data, it is suspected that most children with UTI can be expected to improve within 48 to 72 hours of starting treatment.[756,757] In the observational study published by Karavanaki et al. (2019), 148 children under 2 years old (median age = 2.4 months) with febrile UTI were observed. Fever after the initiation of treatment lasting longer than 48 hours was associated with an increased incidence of permanent renal lesions as demonstrated on DMSA conducted 6 months after the UTI (RD = 25.4%, p = 0.048). Using multivariable logistic regression, delay in treatment initiation of over 72 hours, presence of vesicourinary reflex (VUR), older age, and higher infection severity appeared to be more significant predictors of development of renal lesions when compared with fever duration after initiation of treatment. In concordance with the study by Karavanki et al. (2019), a review on UTIs in children published by Tullus and Shaikh (2020) suggest that the most common reasons for lack of clinical improvement during the first 48 to 72 hours include malformations of the urinary tract, other genitourinary abnormalities (e.g., VUR, renal abscess, hydronephrosis, etc.), incorrect diagnosis, and/or an antimicrobial resistant pathogen.[756] As such, authors believe it is reasonable to pursue additional work-up, including non-invasive imaging such as renal and bladder ultrasonography (RBUS) to check the patient for some of the above common reasons for treatment failure if no clinical improvement is observed during this timeframe. Historically, (and in the most recently published American Academy of Pediatrics (AAP) guidelines on UTI for children published in 2016) RBUS is suggested for all infants with febrile UTI under 2 years old in order to detect management-altering abnormalities.[758–761] It should be noted that many studies have questioned the utility of routine use in early illness.[218,751,762] Some animal data suggest that endotoxin from some common uropathogens such as *Escherichia coli* may produce GU dilatation during acute infection and may theoretically be misattributed to hydronephrosis or obstruction based on RBUS imaging.[763] Additionally, changes in the size and shape of the renal parenchyma due to edema or inflammation are common during acute infection.[218] As such, it seems reasonable to let severity of illness be an important factor when deciding when RBUS should be conducted if it is indicated; critical illness may warrant earlier imaging while patients who have a lower severity of illness and/or rapidly improve over the first 48 hours can likely have their imaging deferred to a later time in order to minimize the chances of the aforementioned physiologic confounders that may result in misleading findings. Recognizing that some commons reasons for recurrent UTI or treatment failure in children such as VUR may not always be detected by RBUS, more invasive

imaging techniques such as voiding cystourethrography (VCUG) or nuclear medicine scans may be reasonable at the discretion of the treating clinician(s). Available guidelines also recommend that all infants sustaining febrile UTI should have urine cultures obtained during subsequent febrile illnesses. While this recommendation only qualifies as evidence level C (low) in the AAP guidelines, this is still an additional management item to consider during follow-up visits.[218]

Assuming the patient clinically improves as expected, our authors prefer the evidence-based durations for cystitis and pyelonephritis discussed in questions 19 and 20 in contrast to the most recent AAP guidelines for UTI which recommend early treatment with 7-14 days of antibiotics (based primarily on results of several small RCTs in the 1970s and 1980s, including several that compared single dose regimens to durations of 7 to 10 days) as well as close follow up, as the risk of renal scarring increases as the number of UTI recurrences increases.[218] The SCOUT, STOP, and observational studies that support the practice of not using 10-14 days of treatment were not available at the time of the guideline publication for assessment and incorporation into recommendations. We do respectfully dispute the guideline's assertion that "there are minimal harm and minor cost effects of antimicrobial choice and duration of therapy" but believe 7 days is not an unreasonable empiric duration for febrile UTI in children when differentiation between cystitis and pyelonephritis is challenging based on data discussed in questions 19, 20, and 30.[290,291] The authors also believe it is reasonable to perform antibiotic de-escalation (or "narrowing" of treatment) as soon as culture and susceptibility results are available owing to the benefits and safety of this practice discussed in question 27 and in some studies of hospitalized children.[764–769] .

Overall Conclusion

Most children with UTI are expected to improve on treatment within 48 to 72 hours. Lack of clinical improvement, specifically lacking resolution of fever, seems to warrant additional work-up to detect underlying issues that may contribute to the lack of improvement and/or an increased risk for permanent renal lesions. Patients who improve as expected in the first 48 to 72 hours can receive evidence-based durations based on their suspected infection (e.g., cystitis, pyelonephritis) and it seems reasonable to perform de-escalation at the time of culture and susceptibility result availability.

Q32: For kidney transplant recipients, what is the significance of a positive urine culture?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

UTIs are an important post-transplant complication. [770,771] The spectrum of causative microorganisms is broad and includes typical uropathogens, atypical pathogens and multi-drug resistant organisms.[772] This complexity demands a nuanced understanding of microbial behavior in the context of immunosuppressed individuals. Cultures need to be interpreted within their clinical context, including specific timing post-transplantation and symptoms. Routine treatment of ASB in renal transplant recipients increases colonization with resistant organisms without providing clear benefit and should be avoided after the first two months from transplantation.[773]

Overall Summary

UTIs are an important post-transplant complication, posing a threat to the fragile balance that defines the post-transplant period.[770,771] Altered urinary tract anatomy, compromised immune response, and presence of implants such as urinary catheters and stents create an environment ripe for microbial colonization. Moreover, the spectrum of causative microorganisms extends beyond typical uropathogens, encompassing MDR organisms.[772] Cultures need to be interpreted within their clinical context, including specific timing post-transplantation and symptoms (Figure 9). This complexity demands a nuanced understanding of microbial behavior in the context of immunosuppressed individuals. Cultures are required for both cystitis and pyelonephritis, but blood cultures are recommended for pyelonephritis. Diagnostic considerations, including allograft biopsy for progressive renal failure and the use of specialized culture media for atypical pathogens, may also be needed in kidney transplant recipients (Figure 9).

Several studies have investigated the efficacy of treating ASB in kidney transplant recipients. A randomized controlled trial of 80 patients found that treating AB in the first 2 months post-renal transplantation did not reduce UTIs and may increase their frequency.[770] Another multicentre trial with 199 participants showed no significant difference in symptomatic UTIs between those treated with antibiotics and those who were not, while antibiotic use increased resistant bacterial strains.[774] A study with 205 renal transplant recipients found no benefit in preventing acute graft pyelonephritis through antibiotic treatment of ASB, instead noting increased antibiotic resistance.[775] Similarly, a trial involving 112 renal transplant recipients indicated no significant difference in acute pyelonephritis occurrence or secondary outcomes between treated and untreated groups.[776] Based on these studies, routine screening and treatment of ASB beyond the second month post-transplantation should not be performed. However, given the heterogeneity of the populations in these studies and the variability in immunosuppression, cultures need to be interpreted within their clinical context and individual patient factors.

Table 25. Risk factors for specific microorganisms as uropathogens in the post-transplant period.

Microorganism	Reference	Risk factors	Reference
Gram-positive		Pre-operative	
Staphylococcus spp.	Fernandez	Female	(olenski, fernandez)
Streptococcus spp.	Fernandez	Diabetes mellitus	(olenski), fernandez
Gram-negative		Presence of urological abnormalities	(olenski) fernandez
Escherichia coli	(olenski) Fernandez	Age	Fernandez

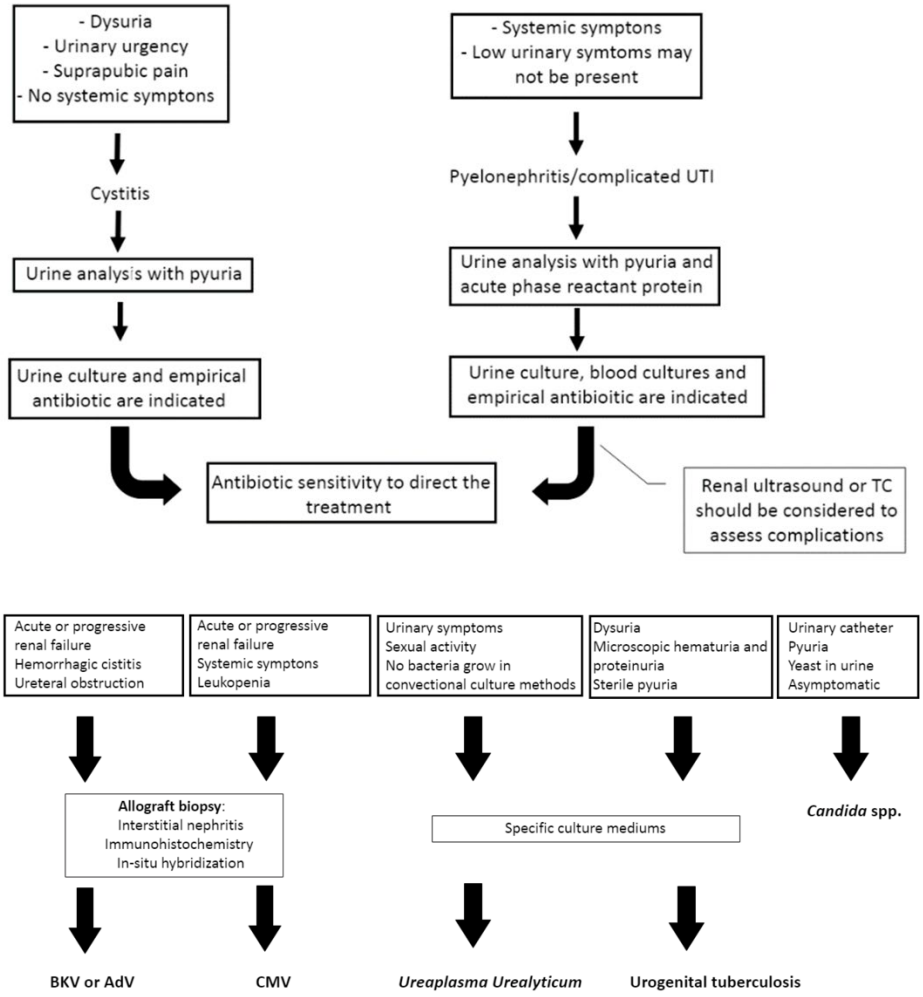
Pseudomonas aeruginosa	(olenski) Fernandez	History of recurrent utis or polycystic kidney disease	Fernandez
Enterobacter spp.	(olenski)	Disused bladder	
Klebsiella spp.	(olenski) Fernandez	Time in dialysis	
Acinetobacter spp.	Fernandez	Lower urinary tract dysfunction	
Citrobacter spp.	Fernandez		
Proteus mirabilis	Fernandez	Intra-operative	
Serratia marcescens	Fernandez	Post-operative	
Raoultella planticola		Vesicoureteric reflux	
Atypical bacteria		Bladder dysfunction	
Ureaplasma spp	Fernandez	Delayed graft function	
Fungal		Prolonged bladder catheterization	
Candida spp.	Fernandez	Ureteral stent (>14–21 days)	
Other pathogens		Immunosuppression (Thymoglobulin, mycophenolate)	
BK virus	Fernandez	Long hospitalization	
Cytomegalovirus	Fernandez	Episodes of acute rejection	
Tuberculosis	Fernandez	Diabetes mellitus post-transplantation	
Adenovirus	Fernandez		
Corynebacterium urealyticum	Fernandez		

Table 26. Diagnostic criteria for UTI within the post-transplant period.

	Asymptomatic	Simple cystitis	Acute Pyelonephritis/ Complicated UTI	Recurrent UTI	Reference
Urine culture	$>10^5$ bacteria CFU/ml.	$>10^3$ bacteria	$>10^4$ bacteria CFU/ml.	$>10^3$ or 10^4 bacteria CFU/ml	Fernandez

		CFU/ml.		according to the type of UTI.	
Clinical presentation		Dysuria, urinary urgency and/or frequency or suprapubic pain. No systemic symptoms and no indwelling urinary catheters.	Fever, chills, malaise, hemodynamic instability; flank/allograft pain or bacteremia with the same organism as in urine. Abnormalities of the genitourinary tract and/or indwelling urinary catheters. Low urinary symptoms may or may not be present.	≥3 utis in prior 12-month period or ≥2 utis in the last 6 months.	Fernandez
Treatment		Outpatient treatment. 7–10 days in the first 6 months post-transplant. 5–7 days beyond 6 months.	Hospitalization required for 14–21 days. In severe infection, reduction/discontinuation of immunosuppression should be considered.	Longer time of treatment (4–6 weeks) and lower dose of prophylaxis after. Evaluation of possible causes. Non-antimicrobial prevention strategies	Fernandez

Figure 9. Proposed assessment framework for patients with suspected urinary tract infection in the post-transplant period.



Overall conclusion

UTIs can be caused by a wider variety of organisms in transplant recipients. Cultures need to be interpreted within their clinical context, including specific timing post-transplantation and symptoms.

Q33: What is the empiric and definitive treatment of emphysematous cystitis and pyelonephritis?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

The treatment of emphysematous cystitis and pyelonephritis lacks robust data, with recommendations mostly relying on clinical judgment and case studies.[777] Early appropriate

antibiotics targeting common pathogens like *E. coli* and *Klebsiella* spp. is reasonable, with a general treatment approach mirroring that for non-emphysematous UTIs.[778] While most cases respond to medical therapy, severe instances may need surgical intervention. Percutaneous catheter drainage, along with antibiotics, shows lower mortality for emphysematous pyelonephritis and is advisable in severe cases to include broader coverage until culture results are available.[779] Most authors feel a treatment duration of 7-14 days (adjusted per clinical response) is reasonable.[780]

Overall summary

Emphysematous cystitis and pyelonephritis are variable clinical entities, but emphysematous pyelonephritis in particular could increase mortality rates up to 14-20% in some studies.[777] A paucity of data exists regarding the optimal treatment of emphysematous cystitis and pyelonephritis. Currently, treatment is guided by clinical experience, case reviews, and case reports. Empiric treatment should be guided by local susceptibility patterns targeted at common uropathogens which cause emphysematous cystitis, including *Escherichia coli* (50-70%) and *Klebsiella pneumoniae* (10-20%). *Enterococcus spp*., obligate anaerobes, and *Pseudomonas aeruginosa* are rarely implicated in emphysematous cystitis and thus, do not require routine empiric coverage in hemodynamically stable patients. [777,780–783] In cases of emphysematous cystitis and pyelonephritis, prompt initiation of intravenous or oral antibiotics likely to attain pharmacokinetic targets is crucial. Available descriptive literature indicates that most emphysematous cystitis cases respond well to medical therapy alone, involving a combination of antibiotics, bladder drainage, and comorbidity management. [777,780–783] In severe or refractory cases, surgical intervention may be warranted.[777,781,784,785] The optimal duration of antimicrobial therapy is not well understood. In general, treatment similar to patients with other more severe UTIs, including febrile or bacteremic UTI or pyelonephritis seems reasonable. Grupper et al (2007) conducted a comprehensive review of fifty-three cases, revealing that the median length of treatment was 10 days, with detailed analysis available for twenty cases.[781] This finding underlines the need for further exploration into the ideal duration of therapy.

For emphysematous pyelonephritis, various treatment strategies have been explored, encompassing medication management alone, medication management combined with percutaneous catheter drainage, medication management alongside emergency nephrectomy, and percutaneous catheter drainage combined with medication management and emergency nephrectomy. Percutaneous catheter drainage is suggested for patients with localized areas of gas and functioning renal tissue and should be considered along with medical management as an initial treatment strategy.[779,783] A systematic review and meta-analysis by Aboumarzouk et al (2014) found percutaneous catheter drainage and medication management were associated with significantly lower mortality rates as compared to emergency nephrectomy.[786]

Similar to emphysematous cystitis, it is reported that emphysematous pyelonephritis is commonly caused by *Escherichia coli* (49%–67%) and *Klebsiella pneumoniae* (20%–24%). *Proteus spp.* (5%–18%), *Enterococcus spp.* (14%), and *Pseudomonas aeruginosa* (5%) are also reported in literature.[787] Therefore, when initiating empiric antimicrobial therapy, it is crucial to target these prevalent organisms with reliable antimicrobials based on local susceptibility patterns. In cases where patients are present with septic shock or severe disease, it is reasonable

to include expanded coverage for E*nterococcus* spp. and *P. aeruginosa* infections until culture results are available. This proactive approach ensures that the treatment regimen is broad enough to address potentially complicated factors, thereby potentially enhancing the patient's chances of recovery. Like with emphysematous cystitis, the optimal duration of treatment for emphysematous pyelonephritis is unknown. Findings from Wu et al suggest that a reasonable approach is to align the duration of therapy with that of other complicated UTIs and pyelonephritis.[778] Treating emphysematous pyelonephritis similar to patients with other more severe UTIs, including febrile or bacteremic UTI with individualized adjustments based on the patient's clinical response seems reasonable.

Overall conclusion

Emphysematous cystitis and pyelonephritis may respond to medical therapy. However, severe instances may need surgical intervention for source control.

Q34: What is the clinical presentation and diagnostic approach for renal or perinephric abscess? What is the empiric and definitive treatment of renal abscess and perinephric abscess?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Perinephric abscesses are serious conditions with varied presentations.[788] Typical symptoms include lumbar pain and fever, with many patients presenting with costovertebral angle tenderness. CT imaging is crucial for diagnosis and management, which may include medical therapy, percutaneous drainage, or surgery for refractory cases.[788] These abscesses are commonly caused by gram-negative bacteria or hematogenous seeding from organisms like Staphylococcus aureus. Decision to opt for drainage of the abscess if often influenced by the size[789,790], however some form of drainage is often necessary for definitive treatment. Further research is needed on optimal source control intervention strategies and when medical management alone may be used.[791–793]

Overall summary

Perinephric abscesses have historically posed a significant challenge in urologic practice, marked by a high mortality rate.[794] Consequently, healthcare professionals must maintain a heightened level of vigilance and ensure a prompt diagnosis.[793,795] These findings can present as an acute emergency or as an insidious chronic condition[796], with atypical indolent presentations occasionally in older adults or autonomic neuropathy patients.[793,797–799] A study conducted in China revealed that the most common symptoms on presentation included lumbar pain and fever, with a striking 87.8% of patients exhibiting CVA tenderness.[800] Furthermore, perinephric abscess should be suspected in patients diagnosed with pyelonephritis who show a delayed response to initial antimicrobial therapy, underscoring the need for careful consideration and thorough evaluation in such cases.

Perinephric abscesses can develop due to various causes, including gram-negative enteric organisms, polymicrobial infections, or hematogenous seeding from *Staphylococcus aureus*.[800,801] Urine studies can occasionally be normal in cases of perinephric abscesses that were inoculated from hematogenous sources, such as *S. aureus* bacteremia.[802] To accurately diagnose and assess the extent of perinephric abscesses, CT imaging is widely considered the most effective modality and can elucidate spread to adjacent vital structures and differentiate abscess from other similar findings including renal cell carcinoma and emphysematous pyelonephritis.[803] With regards to renal abscesses, occasionally "lobar nephronia" can be visualized, though only most accurately in the setting of contrast-enhanced imaging.[804]

The management of renal abscesses poses a complex challenge in clinical practice. While there are instances where medical management alone suffices[793], percutaneous drainage often becomes a necessary intervention for both renal and perinephric abscesses, contributing to decreased morbidity rates.[788] For renal abscesses, the decision to opt for drainage can be influenced by the size of the abscess, particularly in cases where the abscess measures less than 5 cm.[789,790] Limited data is available regarding the sole use of medical management for perinephric abscesses. However, certain observational studies suggest that this approach might be viable for very small abscesses.[791,792] Very limited evidence, primarily surgical, also exists for management of abscesses with septations, as well as ideal candidates for nephrectomy in setting of refractory cases; as emphasized by Rubilotta et al (2014), prospective randomized studies are imperative to provide definitive answers to these critical questions, highlighting the pressing need for further research in the field of renal abscess management.[788]

Based on the microbiologic patterns, empiric antibiotic therapy should initially target gram negative and Staph species. If a patient is clinically stable, one might consider temporarily delaying antibiotics if drainage can be performed promptly, as perinephric abscesses do not always communicate with the collecting system and an aspiration may be the only microbiologically informative specimen. Future prospective trials may consider ideal antibiotic duration for renal and perinephric abscesses, as expert opinion does not distinguish between 14 to 21 days of recommended therapy.[802] Additionally, limited evidence exists regarding ideal timing of catheter placement, which will be elaborated upon in the following section.

Overall Conclusion

Perinephric abscesses may require CT imaging for diagnosis and management. In addition to antimicrobials, percutaneous drainage or surgery may be needed for refractory cases.[788]

Q35: What is the clinical presentation, diagnostic approach, and treatment for acute and chronic prostatitis?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP) are inflammatory prostate syndromes with ABP often presenting abruptly with febrile UTI symptoms and CBP involving more persistent symptoms or recurrent UTIs.[805,806] Diagnosis for ABP relies on clinical presentation and laboratory tests. CBP diagnosis involves comparing bacteria levels in prostatic fluid and urinary cultures, yet definitive testing is debated. Testing for prostate specific antigen (PSA) appears of limited utility.[807] Maneuvers to express prostatic fluid, such as prostate massage, are of limited clinical utility and urology consultation may be needed.[807,808] The optimal durations of treatment for ABP or CBP are unknown and have not been established by high-quality studies. Additional prospective studies are needed to determine the appropriate duration of treatment for ABP and CBP.

Overall Summary

Table 27. Definitions of prostatitis based on chronicity.	
Acute bacterial prostatitis	**Chronic bacterial prostatitis**
An acute, clinically manifest infection of the prostate for which a bacterial causative agent is either highly suspected or established.	A prostate infection characterized by chronic or recurrent urogenital symptoms lasting for over three months, with evidence of bacterial infection of the prostate.

Acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP) are two established inflammatory syndromes of the prostate, also known as "Type I Prostatitis" and "Type II Prostatitis", respectively, according to the US National Institutes of Health.[809] However, it should be noted that bacterial infections of the prostate are estimated to be a minority of prostatitis syndromes.[809] In a retrospective study of 409 men with prostatitis syndromes, only 10% had positive bacterial cultures of prostatic fluid, which included atypical bacteria.[810]

Acute Prostatitis: Clinical Presentation, Diagnostic Approach, and Treatment

Limited evidence exists for the diagnostic evaluation of acute bacterial prostatitis, primarily relying on a clinical and laboratory-driven approach. The true incidence of ABP remains unknown. ABP typically manifests as a febrile UTI with an abrupt onset of systemic symptoms (fever, chills, malaise, nausea, vomiting) and lower urinary tract symptoms (dysuria, frequency, urgency). Suprapubic, pelvic, or perineal pain is common. In notable studies, fever was observed in 80% of hospitalized patients [805] and in 34% of those diagnosed in the emergency department.[811] Urinary symptoms were prevalent in over 70% of cases. Notably, bladder outlet obstruction was not a common factor in ABP, although it could manifest in over 20% of patients as a symptom, with 9% presenting with acute urinary retention. Pelvic pain was reported in 43% of patients. Digital rectal exam (DRE) aids diagnosis, revealing abnormalities in over 80% of cases, including an enlarged tender prostate in more than 90% of patients.[805,811] A history of UTI was noted in 37% of patients, and relapse occurs in 5-10% of cases.[812–814] Prostatic massage during DRE is often avoided due to discomfort and lack of clear diagnostic benefit.

Urine analysis and culture are valuable in diagnosing ABP, with urine culture being particularly significant. A study by Etienne et al (2008) found that nitrite and leukocyte dipstick testing together

had a positive predictive value of 95% and a negative predictive value of 70%, aiding in ABP diagnosis, although less helpful in excluding it, especially when compared to typical UTI cases in women.[815] Contrarily, testing serum PSA levels lacks diagnostic benefit. Although PSA levels might be elevated in around 60% of ABP cases and 20% of chronic bacterial prostatitis (CBP) cases, elevated PSA levels can occur for various reasons unrelated to ABP or CBP. Despite fluctuations in PSA levels during ABP's clinical course (as demonstrated by Gamé et al in 2003), practical diagnostic information from these fluctuations remains unproven.[807]

Some patients, particularly those immunocompromised, may be more susceptible to the development of prostatic abscesses. [816,817] Prostatic abscess formation is rare, but incidence rates vary. In one prospective study of 45 men hospitalized for ABP who underwent transrectal ultrasonography of the prostate, no lesions suggestive of prostatic abscess were identified.[818] Another small prospective study reports a frequency of prostatic abscess of 7.1% (2 patients out of 28) in men over 50 years old with ABP and persistent fever.[819] Cho et al (2005) analyzed the clinical records of 335 patients in a multicenter study and found a prostatic abscess rate of 3.1% (4 out of 130).[820] In another, larger, prospective study comprising 614 patients diagnosed with ABP, the incidence of prostatic abscess was 2.7%.[811] Recent observational studies report relapse rates between 5% and 10%.[812–814] Marquez-Algaba et al (2021) found that diabetes, benign prostate hypertrophy, incontinence, and a history of prior UTI seem to be risk factors for relapse or progression to chronic prostatitis.[812]

ABP treatment is based on antimicrobial therapy and supportive measures, like other complicated UTIs. However, longer courses of antibiotics are often prescribed despite limited evidence of accrued benefit. Only one RCT in Romania, possibly still ongoing, has attempted to compare two different antimicrobials in ABP: levofloxacin and cefixime.[821] However, the trial’s objectives and methods render the trial difficult to interpret, despite the authors mentioning that both antibiotics were equally effective. There is no high-quality evidence to support the optimal antibiotic choices in ABP. Prostatitis, much like other UTIs, is typically treated empirically pending culture results. Once culture and susceptibility data are available, antibiotic therapy can be tailored. In one prospective cohort study, patients whose treatment was not tailored had a significantly increased risk of relapse (as discussed later in this section).[812]

Traditionally, fluoroquinolones have been preferred for both outpatient and inpatient treatment of ABP due to their favorable pharmacokinetics, achieving high prostatic fluid and tissue levels in situations without acute inflammation.[822] However, the emergence of quinolone-resistant pathogens, observed in 40% of cases in a recent study has raised concerns.[812] *Escherichia coli* was the most common isolated pathogen in community-acquired ABP (67.5%) and *Pseudomonas aeruginosa* in healthcare-associated ABP (18.5%). Notably, patients adequately treated with tailored fluoroquinolones or intravenous β-lactams had a lower risk of relapse compared to those given oral β-lactams or trimethoprim/sulfamethoxazole. However, causal associations remain unproven, necessitating further prospective RCT led trials to establish the superiority of fluoroquinolones. B-lactams with varied pharmacokinetic profiles, such as piperacillin, ceftriaxone, and ceftazidime exhibit reasonable prostatic penetration, however again there are no comparative or prospective data to inform how clinical outcomes compare between β-lactams and fluoroquinolones. Efficacy of aminoglycosides remains uncertain, however intramuscular gentamicin combined with a β-lactam showed some level of symptom improvement in cases in

which fluoroquinolones were contraindicated or found to have no *in vitro* activity against the isolated organism.[823] Based on a small prospective study and case report, oral or intravenous fosfomycin may be an option for ABP treatment.[824,825]

In patients meeting sepsis criteria or who cannot take oral treatment warranting parenteral therapy, intravenous fluoroquinolones or expanded spectrum cephalosporins (e.g., ceftriaxone) are commonly used, with or without an aminoglycoside. In situations where drug-resistant pathogens are likely (e.g., recent history of infections with drug-resistant organisms), empiric treatment individualized to the patient's recent microbiology data is reasonable pending new culture and susceptibility testing. UTIs due to MDR organisms are an increasing problem worldwide[826] and thus, is also a concern in the management of ABP. Especially problematic is the increasing resistance to the historically preferred treatment class of fluoroquinolones.[827] Common empiric regimens for ABP are also generally active against *N. gonorrhoeae* and *C. trachomatis* and could be considered as potential pathogens in patients who may have been exposed to sexually transmitted infections.

The optimal duration of treatment for ABP is not established by high-quality data. Traditionally, due to theoretical concerns about antimicrobial penetration into prostatic tissue and eradication of prostatic infectious foci, the recommended duration of treatment has been at least 2 weeks. Some argue that shorter durations of therapy have been associated with progression to chronic symptoms. This statement is based on 2 RCTs in men with recurrent UTI, in which the context differed markedly (one studied invasive infections).[828,829] In both studies the follow-up period was relatively short and relapse rates were 68% and 93%, respectively. On the other hand, a recent 2021 prospective study report a much lower relapse rate of 6.3%[812], similar to the 5% to 10% published in two other observational studies.[813,814] Of note, the PROSTASHORT study published in 2023, contrary to its name, tried to exclude prostatitis among the population of men with febrile UTI.[114] While it is possible that some cases of prostatitis were enrolled and both the 7-day and 14-day arms had remarkably high treatment success rates (95.6% and 100%, respectively), clinical success was defined as only lack of fever, not resolution of urologic symptoms. Additionally, an incredibly small dose of ofloxacin was used that still produced robust clinical response. Additional prospective studies are warranted to determine the optimal duration of treatment for ABP.

Chronic Prostatitis: Clinical Presentation, Diagnostic Approach, and Treatment

There is no consistent source of evidence describing clinical presentation for CBP. Most literature tends to cite clinical reviews. CBP varies in clinical presentation, often involving persistent urogenital symptoms or recurrent symptomatic episodes of UTI caused by the same organism. Some patients are said to be asymptomatic but lower urinary tract cultures can document persistent or recurrent bacteriuria.[809]

The diagnostic standard for CBP is the detection of higher levels of bacteria in prostatic fluid compared to samples from the urethra and bladder in symptomatic patients. However, this has not been validated in a randomized fashion. Diagnostic approach consists in doing quantitative bacteriological localization cultures and microscopy of the segmented urine and expressed prostatic secretion (EPS). Such segmented microbiological analysis of the lower urinary tract is commonly referred to as the "four-glass test".[830] A simplified version of this test based on

bacteriological culture of the pre-massage and post- prostatic massage voided urine (the "two-glass" assay) has been proposed as an alternative test.[831] However, in a study comparing the tests, the two-glass test detected uropathogens in fewer cases (44%) compared to the standard four-glass test.[831] Maneuvers to express prostatic fluid, typically performed only by urologists, seem to be rarely performed in clinical practice. In one survey of 504 urologists (64% response rate), more than 75% of responders said that they never or rarely perform the four-glass test.[806] Moreover, test results did not seem to influence the use of antibiotics. Instead, the diagnosis of chronic bacterial prostatitis is typically presumptive, particularly if bacteriuria is also present. The measurement of prostate specific antigen (PSA) levels has not been shown to provide clinical utility. In a subset analysis of a RCT of 377 patients diagnosed with chronic bacterial prostatitis; only about 20% had increased PSA. [832]

Overall Conclusion

ABP and CBP are complexe inflammatory prostate syndromes that range from acute symptoms to persistent and recurrent symptoms and complications.[805,806] Diagnosis relies on clinical presentation and laboratory tests. The diagnosis of CBP requires comparing bacterial levels in prostatic fluid and urinary cultures, yet definitive testing is debated. The optimal durations of treatment for ABP or CBP are unknown.

Q36: What is the optimal clinical approach for patients with nephrolithiasis, foreign objects, nephrostomy tubes, and/or ureteral stents?

Clear recommendation

Executive Summary

Routine cystoscopy and urodynamic studies do not require antimicrobial prophylaxis in asymptomatic patients. Pre-operative antibiotics do not appear to reduce infectious complications from routine cystoscopic stent removal nor nephrostomy tube placement.[833,834] The majority of patients with uncomplicated urologic cases undergoing percutaneous nephrolithotomy, a single dose of antimicrobial prophylaxis appears to reduce the risk of infection.[108,464,835,836] However, in a recent meta-analysis, single dose was found to be associated with higher rates of SIRS post nephrolithotomy compared with extended perioperative dosing in "high risk" patients; however, the use of a non-specific measure such as SIRS to detect complications may overidentify complications.[837,838] If there are particularly vulnerable patients, such as in pregnancy or renal transplant, extended pre-operative dosing schedules are reasonable to consider. Published RCTs use a 7-day duration pre-operatively, however it is unclear if that long of a course is routinely necessary.[839,840]

Overall summary

The American Urological Association and the European Association of Urology both specifically identify systemic antimicrobial usage as the primary driver for antimicrobial resistance and that they should only be used when medically indicated.[464,473] In general, existing urologic

guidelines suggest that invasive procedures be delayed if the patient has an active infection, which is reasonable, however it should be noted that delaying definitive procedures that would address a pathophysiologic process that ultimately led to the infection in the first place may increase the risk for infectious complications.

Percutaneous nephrolithotomy

For the majority of patients with uncomplicated urologic cases undergoing nephrolithotomy (PCNL), a single dose of an antimicrobial within 1 hour of an incision (prior to the procedure start) appears sufficient and is proposed by both the AUA and EAU guidelines. Antimicrobial prophylaxis appears to reduce the rate of fever after PCNL even amongst patients without positive urine cultures.[841] One RCT showed no benefit from three days of prophylactic antibiotics in PCNL patients with negative urine cultures, as opposed to a single perioperative dose.[835] Two randomized studies (one in which patients received a week of ciprofloxacin prior to the procedure and the other in which patients received a week of nitrofurantoin prior to the procedure) suggest that in certain patients, a course longer than a single dose prior to the procedure may provide a reduction in risk for the development of "SIRS."[839,840] Another RCT comparing a single dose of cefotaxime to no prophylaxis did not find a difference in infectious complications after PCNL, but was underpowered.[842] Additionally, a small prospective cohort study comparing a single dose of IV ciprofloxacin with 3 to 5 days of oral ciprofloxacin or no prophylaxis found lower rates of post procedure UTI in the groups that received antibiotics, but the lowest was seen in the single dose IV group.[836] A more recent meta-analysis of 10 studies (7 small RCTs, 3 retrospective studies) did not find a difference between single dose and extended perioperative (either extended before and/or after procedure) dosing with regard to the rate of fever (7 studies: OR = 0.96, 95% CI: 0.44 to 2.13). Single dose was found to be associated with higher rates of SIRS compared with extended perioperative dosing in "high risk" patients (7 studies: OR = 3.53, 95% CI: 1.91 to 6.54).[837] The definition of patients at "high risk" for PCNL complications were heterogenous, but included patients with larger stones, hydronephrosis, and immunosuppressed patients. Additionally, the implications of using a non-specific collection of symptoms such as SIRS as a measure of complications may result in the overidentification of post-PCNL complications.[838] It has been noted that other non-antibiotic related factors have been strongly associated with the development of post-PCNL fever, such as high volumes of irrigation fluid use.[843]

The optimal duration of antimicrobial prophylaxis for PCNL remains uncertain and warrants additional rigorous study. In the meantime, authors feel it is reasonable to use a single dose of prophylaxis aimed at the most likely pathogens based on regional ecological trends or the patient's unique microbiological history for most patients undergoing PCNL. If there are particularly vulnerable patients, such as renal transplant recipients, extended pre-operative dosing schedules are reasonable to consider. Published RCTS use a 7-day duration pre-operatively, however it is unclear if that long of a course is routinely necessary.[839,840]

Insertion or manipulation of catheter or drain tubing, stents, and/or nephrostomy tubes

In a prospective cohort study of 192 patients who underwent flexible cystoscopy for ureteral stent removal without antibiotic prophylaxis, 21 (10.9%) developed a febrile UTI within the 28-

day follow-up period.[844] About 29% of the 21 patients who developed febrile UTI during the follow-up period had asymptomatic bacteriuria prior to the stent removal. A small RCT of 58 patients who underwent removal of a ureteral stent placed during stone surgery were randomized to receive a single dose of oral ciprofloxacin (500 mg) or no prophylaxis.[833] Positive urine culture rate before stone surgery was 16.7% in the ciprofloxacin group and 11.8% in the no prophylaxis group (p = NS) and at time of stent removal was 16% in the ciprofloxacin group and 11.1% in the no prophylaxis group (p = NS). No patients in either cohort developed symptomatic culture-diagnosed UTI within 1 month of stent removal. This RCT supported a retrospective cohort study published by Abbott et al. (2016) that demonstrated no difference in the rate of infectious complications between patients receiving single dose antimicrobial prophylaxis and patients receiving no prophylaxis.[845] By and large, percutaneous nephrostomy (PCN) tubes are considered safe and effective procedures.[846] While placement of drains may be associated with an increased risk of surgical site infection, RCTs from other (non-urologic) procedures did not find a reduction in the risk for SSI with continuous antimicrobial prophylaxis.[847,848] Additionally, a multicenter prospective study found that out of 145 total insertions or exchanges of ureteral stents or nephrostomies, 122 were performed without antibiotic prophylaxis (54.5% with ASB pre-intervention), post-intervention infectious complications did not differ between patients who received prophylaxis and those who did not.[834] Collectively, this appears to suggest that antimicrobial prophylaxis may not be needed for routine insertion of percutaneous nephrostomy tubes and/or cystoscopic manipulations, such as stent insertion or removal.

Indwelling catheter, nephrostomy tube, or stent duration and risk of infection

It does appear that the longer a stent is in place, that it may confer an increased risk for colonization and possibly, infection. One study suggested four months of dwell time led to triple the risk of febrile UTI, with similar data seen in another study in double J-stent patients.[849] Review and meta-analytic data of ureteral stent removal in kidney transplant patients suggested that less than three weeks of stent dwell time was optimal to prevent risk of stent infection.[850,851] Compared to PCN tubes, some evidence suggests that *Pseudomonas aeruginosa* infections are more likely in stent patients.[846,852] In this context, stent cultures can also sometimes provide unique information. In one study, 33% of stent cultures had additional organisms compared to urethral urine cultures, while negative urine cultures in the setting of positive stent cultures still had 5.7x odds of developing UTI.[853] At the same time, another literature review stated that the causal relationship between ureteral stent colonization and urosepsis still remains to be demonstrated, suggesting that one should also use the patient's context when making decisions.[854] Collectively, these studies may suggest that when a stent is placed for the surgical treatment of a urinary obstruction (e.g., ureteral stones) that definitive stone treatment should ideally occur within a few weeks in order to minimize the risk of subsequent infectious complications. Patients with indwelling urologic hardware appear to be at high risk for multidrug resistant organisms presumably because they are often more commonly have overall higher exposures to systemic antimicrobials.[846] Similarly to stents, individuals with indwelling catheters for extended periods of time appear to be at higher risk for the development of multidrug resistant organisms [846,852,855], as well as an overall increase in the risk for future recurrent infection.[856] Similarly, long term PCN use has been found to increase UTI as well as sepsis risk in certain populations.[857] PCN cultures serve as useful information independent from urethral urine cultures if a patient is symptomatic[858], though no advantage

per literature review is seen if one performs cultures at routine PCN exchanges.[859] These findings stress the importance of regularly re-evaluating the indication for indwelling catheters or nephrostomy tubes and removing them, if able.

Q37: What are non-bacterial causes of urinary tract infections to consider in certain special populations?

Clinical Review (Insufficient Quality of Evidence to Enable a Clear Recommendation)

Executive Summary

Most non-bacterial UTIs are due to *Candida* spp.[860] While 25% of ICU UTIs in the United States are attributed to *Candida* spp., most cases of candiduria are asymptomatic and benign. If symptomatic, fluconazole and amphotericin B are preferred due to favorable urinary pharmacokinetics and pharmacodynamics, but no RCTs are available to determine the best treatment choice or duration.[860,861] Viral UTIs (especially BK polyomavirus and adenovirus) are less common but a noteworthy risk in immunocompromised patients.[862–864] A reduction in the intensity of existing immunosuppression is the primary treatment. Small case reports detail individual experiences with antivirals with *in vitro* activity against these viruses exist, but their retrospective nature and small size limit generalizability.

Overall Summary

Fungal UTI

The majority of non-bacterial UTIs are secondary to *Candida spp., w*hich are common in hospitalized patients.[865] National surveillance studies have estimated that ~25% of UTI in adult icus within the United States are secondary to *Candida* spp.; this number may overestimate the burden of true infection, however, as many patients experience asymptomatic candiduria.[866] Risk factors for candiduria include recent admission to the ICU, exposure to antibiotics, presence of urinary tract devices, and history of diabetes, transplant, or malignancy.[867] Clinical data suggest asymptomatic candiduria is common and usually benign, thus should not be treated (similar to ASB). Unfortunately, a prospective study suggests that overtreatment of asymptomatic candiduria is common, with 33% of asymptomatic patients receiving at least 7 days of treatment.[868] It should be noted that *Candida* has been rarely described to cause localized infections in other parts of the genitourinary tract, such as prostate[869–871], epididymis and testicles[869,872], and kidneys[869,873].

No RCTs have directly compared systemic antifungals for the treatment of symptomatic candiduria. Fluconazole is typically the antifungal of choice, owing to its high degree of active drug excreted into the urine, low cost, and advantageous adverse event profile in comparison to alternatives. Amphotericin B deoxycholate is another alternative for fluconazole resistant *Candida spp*. Other triazoles, echinocandins, and liposomal amphotericin B have lower urinary excretion rates and have historically been avoided for fungal UTI with limited available data to support their use.[860] Several case series have been published describing outcomes of treating symptomatic candiduria with echinocandins and generally demonstrate favorable clinical and

mycological cure rates.[874–882] Echinocandins, despite the expected low levels achieved in the lower urinary tract, appear to be reasonable options for patients who are intolerant of fluconazole, have a fluconazole-resistant *Candida* isolate, and/or cannot tolerate amphotericin B. Echinocandins also achieve quite reasonable tissue concentrations in the kidney and are likely effective for pyelonephritis.[877] No data could be found on the use of flucytosine as monotherapy for symptomatic candiduria.

Likewise, no RCTs have compared different durations of treatment for symptomatic candiduria. IDSA guidance, last updated in 2016, continues to suggest 2 weeks of treatment for both cystitis or pyelonephritis due to *Candida* spp.[883] In a study of asymptomatic or minimally symptomatic patients with candiduria, administration of fluconazole did not result in higher eradication rates at two weeks of follow-up versus placebo, and clinical outcomes were similar between groups.[866] Additionally, investigators found that for most patients with a urinary catheter in the placebo group, removal of the catheter alone resulted in eradication of the *Candida*.
Two weeks of oral fluconazole was associated with higher rates of candiduria clearance in a small sub-group analysis of asymptomatic patients.[866] However, whether that translates to improved clinical outcomes in symptomatic patients is not known. In one case series a single dose of amphotericin B deoxycholate achieved eradication of candiduria in the majority of patients.[884]

Viral UTI

Greater than 80% of the general population are unknowingly BK (named for the patient's initials in whom the virus was first discovered in 1971) polyomavirus (BKV) seropositive.[885] BKV lays dormant in renal tubular and uroepithelial cells following primary infection in immunocompetent people. Asymptomatic viruria occurs in up to 20% of immunocompetent patients and clinically significant reactivation can occur in certain immunosuppressed individuals, with those at highest risk being the kidney transplant population followed by the HSCT population.[862,863,885,886] Studies have found upwards of 50% of kidney transplant patients will experience BKV viruria and one-third will experience BKV viremia following transplant, with the most severe complication being BKV associated nephropathy. Up to 10% of patients may experience BKV nephropathy which can manifest as mildly elevated serum creatinine or allograft failure.[886–889] Other morbidities associated with BKV infection include hemorrhagic cystitis[885,886,890,891] (most commonly observed in the HSCT population), ureteral stenosis[885,886,889,892,893], and a possible contribution to oncogenesis.[863,885,894–896] No systemic antimicrobial therapy has been shown to improve outcomes for the treatment of BKV associated nephropathy or hemorrhagic cystitis; the mainstay of therapy is reduction in the intensity of existing immunosuppression. Agents that have anti-BKV activity *in vitro* and have been studied for treatment include cidofovir, brincidofovir, leflunomide, and fluoroquinolones. These agents have only been studied in uncontrolled, retrospective studies which have yielded conflicting results. [885,888,889]

Adenovirus infection is typically asymptomatic or mild in the immunocompetent population but can cause significant morbidity and mortality in the HSCT and solid organ transplant (SOT) population.[862] It can cause a variety of complications, including some involving the urinary tract such as hemorrhagic cystitis, commonly presenting as gross or microscopic hematuria in

HSCT patients.[862,864] In SOT patients, adenovirus most commonly affects the transplant organ; adenovirus related hemorrhagic cystitis has most commonly been reported in renal transplant patients.[862] Like BKV, a reduction in existing immunosuppression is an important component to treatment.[897] Cidofovir is the most commonly used anti-infective in clinical practice[898–903] for adenovirus related hemorrhagic cystitis, although no prospective data is available to support the practice and there are risks associated with systemic and perhaps even intravesical cidofovir.[899] The predominance of data exists as case reports using cidofovir[898–903] or other treatments (e.g., ribavirin[904–909], hyaluronic acid[910], hyperbaric oxygen[911], alum irrigation[912], ganciclovir[913], brincidofovir[914]) in a variety of HSCT or solid organ transplant adult and pediatric populations.

Overall Conclusion

Most non-bacterial UTIs are due to *Candida* spp. Fluconazole and amphotericin B are preferred treatment agents, but no RCTs are available to determine the best choice or duration.[860,861] Viral UTIs, such as those caused by BK polyomavirus and adenovirus, are primarily a condition in immunocompromised patients primarily treated with a reduction in the intensity of immunosuppression, if possible.

References

1. Stapleton A, Latham RH, Johnson C, Stamm WE. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection: a randomized, double-blind, placebo-controlled trial. *JAMA*. 1990;264(6):703-206.

2. Melekos MD, Asbach HW, Gerharz E, Zarakovitis IE, Weingaertner K, Naber KG. Post-intercourse versus daily ciprofloxacin prophylaxis for recurrent urinary tract infections in premenopausal women. *J Urol*. 1997;157(3):935-939.

3. Jent P, Berger J, Kuhn A, Trautner BW, Atkinson A, Marschall J. Antibiotics for Preventing Recurrent Urinary Tract Infection: Systematic Review and Meta-analysis. *Open Forum Infectious Diseases*. 2022;9(7). doi:https://doi.org/10.1093/ofid/ofac327

4. Buettcher M, Trueck J, Niederer-Loher A, et al. Swiss consensus recommendations on urinary tract infections in children. *Eur J Pediatr*. 2021;180(3):663-674. doi:10.1007/s00431-020-03714-4

5. Autore G, Bernardi L, Ghidini F, et al. Antibiotic Prophylaxis for the Prevention of Urinary Tract Infections in Children: Guideline and Recommendations from the Emilia-Romagna Pediatric Urinary Tract Infections (UTI-Ped-ER) Study Group. *Antibiotics (Basel)*. 2023;12(6):1040. doi:10.3390/antibiotics12061040

6. Mattoo TK, Shaikh N, Nelson CP. Contemporary Management of Urinary Tract Infection in Children. *Pediatrics*. 2021;147(2):e2020012138. doi:10.1542/peds.2020-012138

7. Guibert J, Humbert G, Meyrier A, et al. [Antibioprevention of recurrent cystitis. A randomized double-blind comparative trial of 2 dosages of pefloxacin]. *Presse Med*. 1995;24(4):213-216.

8. Zhong Y, Fang Y, Zhou J, Tang Y, Gong S, Ding X. Effectiveness and safety of patient initiated single-dose versus continuous low-dose antibiotic prophylaxis for recurrent urinary tract

infections in postmenopausal women: a randomized controlled study. *J Int Med Res*. 2011;39(6):2335-2343. doi:doi:10.1177/147323001103900633

9. Stamm WE, Counts GW, Wagner KF, et al. Antimicrobial prophylaxis of recurrent urinary tract infections: a double-blind, placebo-controlled trial. *Ann Intern Med*. 1980;92(6):770-775. doi:10.7326/0003-4819-92-6-770

10. Vahlensieck W, Westenfelder M. Nitrofurantoin versus trimethoprim for lowdose long-term prophylaxis in patients with recurrent urinary tract infections. A prospective randomized study. *Int Urol Nephrol*. 1992;24(1):3-10. doi:doi:10.1007/BF02552109

11. Costantini E, Zucchi A, Salvini E, et al. Prulifloxacin vs fosfomycin for prophylaxis in female patients with recurrent UTIs: a non-inferiority trial. *Int Urogynecol J*. 2014;25(9):1173-1178. doi:10.1007/s00192-013-2318-1

12. Brumfitt W, Smith GW, Hamilton-Miller JMT, Gargan RA. A clinical comparison between Macrodantin and trimethoprim for prophylaxis in women with recurrent urinary infections. *J Antimicrob Chemother*. 1985;16(1):111-120. doi:10.1093/jac/16.1.111

13. Brumfitt W, Hamilton-Miller JM. A comparative trial of low dose cefaclor and macrocrystalline nitrofurantoin in the prevention of recurrent urinary tract infection. *Infection*. 1995;23(2):98-102. doi:10.1007/BF01833874

14. Brumfitt W, Hamilton-Miller JM, Smith GW, al-Wali W. Comparative trial of norfloxacin and macrocrystalline nitrofurantoin (Macrodantin) in the prophylaxis of recurrent urinary tract infection in women. *Q J Med*. 1991;81(294):811-820.

15. Raz R, Boger S. Long-term prophylaxis with norfloxacin versus nitrofurantoin in women with recurrent urinary tract infection. *Antimicrob Agents Chemother*. 1991;35(6):1241-1242. doi:10.1128/AAC.35.6.1241

16. Seppänen J. Cinoxacin vs trimethoprim--safety and efficacy in the prophylaxis of uncomplicated urinary tract infections. *Drugs Exp Clin Res*. 1988;14(10):669-671.

17. NUNEZ U, SOLIS Z. Macrocrystalline nitrofurantoin versus norfloxacin as treatment and prophylaxis in uncomplicated recurrent urinary tract infection. *Curr ther res*. 1990;48(2):234-245.

18. 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;128(3):595-610. doi:10.1542/peds.2011-1330

19. Morello W, Baskin E, Jankauskiene A, et al. Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux. *New England Journal of Medicine*. 2023;389(11):987-997. doi:10.1056/NEJMoa2300161

20. McGuinness 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.

21. Cowan CC, Hutchison C, Cole T, 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. *Clin Oncol (R Coll Radiol)*. 2012;24(2):e31-38. doi:10.1016/j.clon.2011.05.009

22. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol*. 2002;9(3):1558-1562.

23. Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. *Mol Nutr Food Res*. 2007;51(6):738-745. doi:10.1002/mnfr.200600275

24. Howell AB. Bioactive compounds in cranberries and their role in prevention of urinary tract infections. *Mol Nutr Food Res*. 2007;51(6):732-737. doi:10.1002/mnfr.200700038

25. 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 infection1. *The American Journal of Clinical Nutrition*. 2016;103(6):1434-1442. doi:10.3945/ajcn.116.130542

26. Xia JY, Yang C, Xu DF, Xia H, Yang LG, Sun GJ. Consumption of cranberry as adjuvant therapy for urinary tract infections in susceptible populations: A systematic review and meta-analysis with trial sequential analysis. *PLoS One*. 2021;16(9):e0256992. doi:10.1371/journal.pone.0256992

27. Hisano M, Bruschini H, Nicodemo AC, Srougi M. Cranberries and lower urinary tract infection prevention. *Clinics (Sao Paulo)*. 2012;67(6):661-667. doi:10.6061/clinics/2012(06)18

28. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;2012(10):CD001321. doi:10.1002/14651858.CD001321.pub5

29. Mantzorou M, Giaginis C. Cranberry Consumption Against Urinary Tract Infections: Clinical Stateof- the-Art and Future Perspectives. *Curr Pharm Biotechnol*. 2018;19(13):1049-1063. doi:10.2174/1389201020666181206104129

30. Nabavi SF, Sureda A, Daglia M, Izadi M, Nabavi SM. Cranberry for Urinary Tract Infection: From Bench to Bedside. *Curr Top Med Chem*. 2017;17(3):331-339. doi:10.2174/1568026616666160829161031

31. Foxman B, Cronenwett AEW, Spino C, Berger MB, Morgan DM. Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. *Am J Obstet Gynecol*. 2015;213(2):194.e1-8. doi:10.1016/j.ajog.2015.04.003

32. 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. *Clin Infect Dis*. 2011;52(1):23-30. doi:10.1093/cid/ciq073

33. McMurdo MET, 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. *J Antimicrob Chemother*. 2009;63(2):389-395. doi:10.1093/jac/dkn489

34. González de Llano D, Moreno-Arribas MV, Bartolomé B. Cranberry Polyphenols and Prevention against Urinary Tract Infections: Relevant Considerations. *Molecules*. 2020;25(15):3523. doi:10.3390/molecules25153523

35. Gupta K, Chou MY, Howell A, Wobbe C, Grady R, Stapleton AE. Cranberry products inhibit adherence of p-fimbriated Escherichia coli to primary cultured bladder and vaginal epithelial cells. *J Urol*. 2007;177(6):2357-2360. doi:10.1016/j.juro.2007.01.114

36. Fu Z, Liska D, Talan D, Chung M. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. *J Nutr*. 2017;147(12):2282-2288. doi:10.3945/jn.117.254961

37. Wang C. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systemic review and meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172:988-989. doi:doi:10.1001/archinternmed.2012.3004

38. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. *J Urol*. 2008;180(4):1367-1372. doi:10.1016/j.juro.2008.06.016

39. McMurdo MET, Bissett LY, Price RJG, 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):256-261. doi:10.1093/ageing/afi101

40. 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. *J Spinal Cord Med*. 2004;27(1):35-40. doi:10.1080/10790268.2004.11753728

41. 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. *J Spinal Cord Med*. 2004;27(1):29-34. doi:10.1080/10790268.2004.11753727

42. Hess MJ, Hess PE, 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):622-626. doi:10.1038/sc.2008.25

43. Babar A, Moore L, Leblanc V, 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 Urol*. 2021;21(1):44. doi:10.1186/s12894-021-00811-w

44. Sihra N, Goodman A, Zakri R, Sahai A, Malde S. Nonantibiotic prevention and management of recurrent urinary tract infection. *Nat Rev Urol*. 2018;15(12):750-776. doi:10.1038/s41585-018-0106-x

45. Occhipinti A, Germano A, Maffei ME. Prevention of Urinary Tract Infection with Oximacro, A Cranberry Extract with a High Content of A-Type Proanthocyanidins: A Pre-Clinical Double-Blind Controlled Study. *Urol J*. 2016;13(2):2640-2649.

46. P K, S K, Y T, G C, A H. 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). doi:10.1080/14787210.2019.1664287

47. 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. doi:10.1136/bmj.322.7302.1571

48. Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc*. 2012;87(2):143-150. doi:10.1016/j.mayocp.2011.10.006

49. 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):751-754. doi:10.1001/jama.1994.03510340041031

50. Di Martino P, Agniel R, David K, et al. Reduction of Escherichia coli adherence to uroepithelial bladder cells after consumption of cranberry juice: a double-blind randomized placebo-controlled cross-over trial. *World J Urol*. 2006;24(1):21-27. doi:10.1007/s00345-005-0045-z

51. Lee BB, Haran MJ, Hunt LM, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. *Spinal Cord*. 2007;45(8):542-550. doi:10.1038/sj.sc.3101974

52. Bruyère F. [Use of cranberry in chronic urinary tract infections]. *Med Mal Infect*. 2006;36(7):358-363. doi:10.1016/j.medmal.2006.05.001

53. Williams G, Hahn D, Stephens JH, Craig JC, Hodson EM. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews*. 2023;(4). doi:10.1002/14651858.CD001321.pub6

54. Hooton TM, Vecchio M, Iroz A, et al. Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial. *JAMA Intern Med*. 2018;178(11):1509-1515. doi:10.1001/jamainternmed.2018.4204

55. Mentes JC, Culp K. Reducing hydration-linked events in nursing home residents. *Clin Nurs Res*. 2003;12(3):210-225; discussion 226-228. doi:10.1177/1054773803252996

56. Vento KA, Koskan A, Lynch H, Kavouras S, Johnston C, Wardenaar FC. Effect of increased water intake on uropathogenic bacterial activity of underhydrated menstruating young adult women: A randomized crossover trial. *Nutr Health*. Published online October 12, 2022:2601060221129159. doi:10.1177/02601060221129159

57. Friedman SA, Gladstone JL. The effects of hydration and bladder incubation time on urine colony counts. *J Urol*. 1971;105(3):428-432. doi:10.1016/s0022-5347(17)61542-8

58. Cattell WR, Fry IK, Spiro FI, Sardeson JM, Sutcliffe MB, O'Grady F. Effect of diuresis and frequent micturition on the bacterial content of infected urine: a measure of competence of intrinsic hydrokinetic clearance mechanisms. *Br J Urol*. 1970;42(3):290-295. doi:10.1111/j.1464-410x.1970.tb11922.x

59. Tan-Kim J, Shah NM, Do D, Menefee SA. Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women. *Am J Obstet Gynecol*. 2023;229(2):143.e1-143.e9. doi:10.1016/j.ajog.2023.05.002

60. Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis*. 2007;195(5):623-624. doi:10.1086/511526

61. Simunić V, Banović I, Ciglar S, Jeren L, Pavicić Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet*. 2003;82(2):187-197. doi:10.1016/s0020-7292(03)00200-5

62. McVicker L, Labeit AM, Coupland CAC, et al. Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer. *JAMA Oncol*. 2024;10(1):103-108. doi:10.1001/jamaoncol.2023.4508

63. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*. 2018;25(1):11-20. doi:10.1097/GME.0000000000000956

64. Michels TC, Sands JE. Dysuria: Evaluation and Differential Diagnosis in Adults. *Am Fam Physician*. 2015;92(9):778-786.

65. Buck ES, Lukas VA, Rubin RS. Effective Prevention of Recurrent UTIs With Vaginal Estrogen: Pearls for a Urological Approach to Genitourinary Syndrome of Menopause. *Urology*. 2021;151:31-36. doi:10.1016/j.urology.2020.05.058

66. Christmas MM, Iyer S, Daisy C, Maristany S, Letko J, Hickey M. Menopause hormone therapy and urinary symptoms: a systematic review. *Menopause*. 2023;30(6):672-685. doi:10.1097/GME.0000000000002187

67. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol*. 2006;108(6):1354-1360. doi:10.1097/01.AOG.0000241091.86268.6e

68. Mørch LS, Kjaer SK, Keiding N, Løkkegaard E, Lidegaard Ø. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. *Int J Cancer*. 2016;138(6):1506-1515. doi:10.1002/ijc.29878

69. Michaëlsson K, Baron JA, Farahmand BY, Ljunghall S. Use of low potency estrogens does not reduce the risk of hip fracture. *Bone*. 2002;30(4):613-618. doi:10.1016/s8756-3282(01)00701-3

70. ACOG committee opinion no. 556: Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. *Obstet Gynecol*. 2013;121(4):887-890. doi:10.1097/01.AOG.0000428645.90795.d9

71. Mikkola TS, Tuomikoski P, Lyytinen H, et al. Vaginal estradiol use and the risk for cardiovascular mortality. *Hum Reprod*. 2016;31(4):804-809. doi:10.1093/humrep/dew014

72. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*. 1993;329(11):753-756. doi:10.1056/NEJM199309093291102

73. Eriksen B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol*. 1999;180(5):1072-1079. doi:10.1016/s0002-9378(99)70597-1

74. Raz R, Colodner R, Rohana Y, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis*. 2003;36(11):1362-1368. doi:10.1086/374341

75. Dessole S, Rubattu G, Ambrosini G, et al. Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. *Menopause*. 2004;11(1):49-56. doi:10.1097/01.GME.0000077620.13164.62

76. Ferrante KL, Wasenda EJ, Jung CE, Adams-Piper ER, Lukacz ES. Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women: A Randomized Clinical Trial. *Female Pelvic Med Reconstr Surg*. 2021;27(2):112-117. doi:10.1097/SPV.0000000000000749

77. Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer: Clinical Consensus. *Obstet Gynecol*. 2021;138(6):950-960. doi:10.1097/AOG.0000000000004601

78. Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ*. 2022;376:e068229. doi:10.1136/bmj-2021-0068229

79. Botros C, Lozo S, Iyer S, et al. Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial. *Int Urogynecol J*. 2022;33(3):571-580. doi:10.1007/s00192-021-04849-0

80. Chwa A, Kavanagh K, Linnebur SA, Fixen DR. Evaluation of methenamine for urinary tract infection prevention in older adults: a review of the evidence. *Ther Adv Drug Saf*. 2019;10:2042098619876749. doi:10.1177/2042098619876749

81. Li JM, Cosler LE, Harausz EP, Myers CE, Kufel WD. Methenamine for urinary tract infection prophylaxis: A systematic review. *Pharmacotherapy*. 2024;44(2):197-206. doi:10.1002/phar.2895

82. Gu C, Ackerman AL. An oldie but a goodie: Methenamine as a nonantibiotic solution to the prevention of recurrent urinary tract infections. Leong JM, ed. *PLoS Pathog*. 2023;19(6):e1011405. doi:10.1371/journal.ppat.1011405

83. Harding C, Chadwick T, Homer T, et al. Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. *Health Technol Assess*. 2022;26(23):1-172. doi:10.3310/QOIZ6538

84. Wolff BJ, Price TK, Joyce CJ, Wolfe AJ, Mueller ER. Oral probiotics and the female urinary microbiome: a double-blinded randomized placebo-controlled trial. *Int Urol Nephrol*. 2019;51(12):2149-2159. doi:10.1007/s11255-019-02282-3

85. Toh SL, Boswell-Ruys CL, Lee BSB, Simpson JM, Clezy KR. Probiotics for preventing urinary tract infection in people with neuropathic bladder. *Cochrane Database Syst Rev*. 2017;9(9):CD010723. doi:10.1002/14651858.CD010723.pub2

86. Toh SL, Lee BB, Ryan S, et al. Probiotics [LGG-BB12 or RC14-GR1] versus placebo as prophylaxis for urinary tract infection in persons with spinal cord injury [ProSCIUTTU]: a randomised controlled trial. *Spinal Cord*. 2019;57(7):550-561. doi:10.1038/s41393-019-0251-y

87. Abdullatif VA, Sur RL, Eshaghian E, et al. Efficacy of Probiotics as Prophylaxis for Urinary Tract Infections in Premenopausal Women: A Systematic Review and Meta-Analysis. *Cureus*. 2021;13(10):e18843. doi:10.7759/cureus.18843

88. Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. *Cochrane Database Syst Rev*. 2015;2015(12):CD008772. doi:10.1002/14651858.CD008772.pub2

89. Sada RM, Matsuo H, Motooka D, et al. Clostridium butyricum Bacteremia Associated with Probiotic Use, Japan - Volume 30, Number 4—April 2024 - Emerging Infectious Diseases journal - CDC. doi:10.3201/eid3004.231633

90. Beerepoot M a. J, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol*. 2013;190(6):1981-1989. doi:10.1016/j.juro.2013.04.142

91. Stapleton AE, Au-Yeung M, Hooton TM, et al. Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clin Infect Dis*. 2011;52(10):1212-1217. doi:10.1093/cid/cir183

92. Sadeghi-Bojd S, Naghshizadian R, Mazaheri M, Ghane Sharbaf F, Assadi F. Efficacy of Probiotic Prophylaxis After The First Febrile Urinary Tract Infection in Children With Normal Urinary Tracts. *J Pediatric Infect Dis Soc*. 2020;9(3):305-310. doi:10.1093/jpids/piz025

93. Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. *Biol Neonate*. 2002;82(2):103-108. doi:10.1159/000063096

94. Quattrone C, Manfredi C, Napolitano L, et al. D-Mannose Plus Saccharomyces boulardii to Prevent Urinary Tract Infections and Discomfort after Cystoscopy: A Single-Center Prospective Randomized Pilot Study. *Medicina (Kaunas)*. 2023;59(6):1165. doi:10.3390/medicina59061165

95. Ala-Jaakkola R, Laitila A, Ouwehand AC, Lehtoranta L. Role of D-mannose in urinary tract infections – a narrative review. *Nutr J*. 2022;21(1):18. doi:10.1186/s12937-022-00769-x

96. Porru D, Parmigiani A, Tinelli C, et al. Oral D-mannose in recurrent urinary tract infections in women: a pilot study. *Journal of Clinical Urology*. 2014;7(3):208-213. doi:10.1177/2051415813518332

97. Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*. 2014;32(1):79-84. doi:10.1007/s00345-013-1091-6

98. Hayward G, Mort S, Hay AD, et al. d-Mannose for Prevention of Recurrent Urinary Tract Infection Among Women: A Randomized Clinical Trial. *JAMA Internal Medicine*. 2024;184(6):619-628. doi:10.1001/jamainternmed.2024.0264

99. Phé V, Pakzad M, Haslam C, et al. Open label feasibility study evaluating D-mannose combined with home-based monitoring of suspected urinary tract infections in patients with multiple sclerosis. *Neurourology and Urodynamics*. 2017;36(7):1770-1775. doi:10.1002/nau.23173

100. Domenici L, Monti M, Bracchi C, et al. D-mannose: a promising support for acute urinary tract infections in women. A pilot study. *Eur Rev Med Pharmacol Sci*. 2016;20(13):2920-2925.

101. Cooper TE, Teng C, Howell M, Teixeira-Pinto A, Jaure A, Wong G. D-mannose for preventing and treating urinary tract infections. *Cochrane Database Syst Rev*. 2022;8(8):CD013608. doi:10.1002/14651858.CD013608.pub2

102. Lenger SM, Bradley MS, Thomas DA, Bertolet MH, Lowder JL, Sutcliffe S. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;223(2):265.e1-265.e13. doi:10.1016/j.ajog.2020.05.048

103. Lenger SM, Chu CM, Ghetti C, et al. d-Mannose for Recurrent Urinary Tract Infection Prevention in Postmenopausal Women Using Vaginal Estrogen: A Randomized Controlled Trial. *Urogynecology (Phila)*. 2023;29(3):367-377. doi:10.1097/SPV.0000000000001270

104. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases*. 2011;52(5):e103-e120. doi:10.1093/cid/ciq257

105. Bilsen MP, Jongeneel RMH, Schneeberger C, et al. Definitions of Urinary Tract Infection in Current Research: A Systematic Review. *Open Forum Infect Dis*. 2023;10(7):ofad332. doi:10.1093/ofid/ofad332

106. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*. 2005;40(5):643-654. doi:10.1086/427507

107. Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):e83-e110. doi:10.1093/cid/ciy1121

108. Bonkat G, Bartoletti R, Bruyere F. EAU Guidelines on Urological Infections 2022. Published online 2022. Accessed September 20, 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-Infections-2022.pdf

109. Anger J, Lee U, Ackerman AL, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. *J Urol*. 2019;202(2):282-289. doi:10.1097/JU.0000000000000296

110. Kaye KS, Belley A, Barth P, et al. Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA*. 2022;328(13):1304-1314. doi:10.1001/jama.2022.17034

111. Chen L, Hua J, Hong SJ, et al. Comparison of the relative efficacy of β-lactam/β-lactamase inhibitors and carbapenems in the treatment of complicated urinary tract infections caused by ceftriaxone-non-susceptible Enterobacterales: a multicentre retrospective observational cohort study. *J Antimicrob Chemother*. 2023;78(3):710-718. doi:10.1093/jac/dkac448

112. Dunne MW, Aronin SI, Das AF, et al. Sulopenem for the Treatment of Complicated Urinary Tract Infections Including Pyelonephritis: A Phase 3, Randomized Trial. *Clin Infect Dis*. 2023;76(1):78-88. doi:10.1093/cid/ciac704

113. Dunne MW, Aronin SI, Das AF, et al. Sulopenem or Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Women: A Phase 3, Randomized Trial. *Clin Infect Dis*. 2023;76(1):66-77. doi:10.1093/cid/ciac738

114. Lafaurie M, Chevret S, Fontaine JP, et al. Antimicrobial for 7 or 14 Days for Febrile Urinary Tract Infection in Men: A Multicenter Noninferiority Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *Clin Infect Dis*. 2023;76(12):2154-2162. doi:10.1093/cid/ciad070

115. Rouphael N, Winokur P, Keefer MC, et al. Daily fosfomycin versus levofloxacin for complicated urinary tract infections. *mBio*. 2023;14(5):e0167723. doi:10.1128/mbio.01677-23

116. Orenstein R, Wong ES. Urinary Tract Infections in Adults. *American Family Physician*. 1999;59(5):1225-1234.

117. Hung KC, Tsai WW, Hsu CW, Lai CC, Tang HJ, Chen IW. Clinical efficacy and safety of novel antibiotics for complicated urinary tract infection: A systematic review and meta-analysis of randomized controlled trials. *International Journal of Antimicrobial Agents*. 2023;62(1):106830. doi:10.1016/j.ijantimicag.2023.106830

118. Trautner B, Cortes-Penfield N. Clinical Practice Guidelines for the Treatment of Comploicated Urinary Tract Infection (cUTI) in Adults: What they say, and how we got there. Presented at: IDWeek 2023; October 14, 2023; Boston, MA.

119. Klausner HA, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. *Curr Med Res Opin*. 2007;23(11):2637-2645. doi:10.1185/030079907x233340

120. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology*. 2008;71(1):17-22. doi:10.1016/j.urology.2007.09.002

121. van Nieuwkoop C, van't Wout JW, Assendelft WJJ, et al. Treatment duration of febrile urinary tract infection (FUTIRST trial): a randomized placebo-controlled multicenter trial comparing short (7 days) antibiotic treatment with conventional treatment (14 days). *BMC Infect Dis*. 2009;9:131. doi:10.1186/1471-2334-9-131

122. Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection: A Randomized Clinical Trial. *JAMA*. 2021;326(4):324. doi:10.1001/jama.2021.9899

123. Germanos GJ, Trautner BW, Zoorob RJ, et al. No Clinical Benefit to Treating Male Urinary Tract Infection Longer Than Seven Days: An Outpatient Database Study. *Open Forum Infectious Diseases*. 2019;6(6):ofz216. doi:10.1093/ofid/ofz216

124. Bilsen MP, Jongeneel RMH, Schneeberger C, et al. Definitions of Urinary Tract Infection in Current Research: A Systematic Review. *Open Forum Infect Dis*. 2023;10(7):ofad332. doi:10.1093/ofid/ofad332

125. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. *Am Fam Physician*. 2005;71(6):1153-1162.

126. Advani SD, Polage CR, Fakih MG. Deconstructing the urinalysis: A novel approach to diagnostic and antimicrobial stewardship. *Antimicrob Steward Healthc Epidemiol*. 2021;1(1):e6. doi:10.1017/ash.2021.167

127. Bhat RG, Katy TA, Place FC. Pediatric urinary tract infections. *Emerg Med Clin North Am*. 2011;29(3):637-653. doi:10.1016/j.emc.2011.04.004

128. Anfinson TJ, Kathol RG. Screening laboratory evaluation in psychiatric patients: a review. *Gen Hosp Psychiatry*. 1992;14(4):248-257. doi:10.1016/0163-8343(92)90095-r

129. Hooton TM, Roberts PL, Stapleton AE. Asymptomatic Bacteriuria and Pyuria in Premenopausal Women. *Clin Infect Dis*. 2021;72(8):1332-1338. doi:10.1093/cid/ciaa274

130. Bilsen MP, Aantjes MJ, van Andel E, et al. Current Pyuria Cutoffs Promote Inappropriate Urinary Tract Infection Diagnosis in Older Women. *Clinical Infectious Diseases*. 2023;76(12):2070-2076. doi:10.1093/cid/ciad099

131. Foudraine DE, Bauer MP, Russcher A, et al. Use of Automated Urine Microscopy Analysis in Clinical Diagnosis of Urinary Tract Infection: Defining an Optimal Diagnostic Score in an Academic Medical Center Population. *J Clin Microbiol*. 2018;56(6):e02030-17. doi:10.1128/JCM.02030-17

132. Bhavsar T, Potula R, Jin M, Truant AL. Predictability of urinalysis parameters in the diagnosis of urinary tract infection: a case study. *MLO Med Lab Obs*. 2015;47(1):8, 10, 12; quiz 13.

133. Pels RJ, Bor DH, Woolhandler S, Himmelstein DU, Lawrence RS. Dipstick urinalysis screening of asymptomatic adults for urinary tract disorders. II. Bacteriuria. *JAMA*. 1989;262(9):1221-1224. doi:10.1001/jama.262.9.1221

134. Smith P, Morris A, Reller LB. Predicting urine culture results by dipstick testing and phase contrast microscopy. *Pathology*. 2003;35(2):161-165.

135. Van Nostrand JD, Junkins AD, Bartholdi RK. Poor predictive ability of urinalysis and microscopic examination to detect urinary tract infection. *Am J Clin Pathol*. 2000;113(5):709-713. doi:10.1309/428N-60XK-UQ3Q-BXLC

136. Eidelman Y, Raveh D, Yinnon AM, Ballin J, Rudensky B, Gottehrer NP. Reagent strip diagnosis of UTI in a high-risk population. *Am J Emerg Med*. 2002;20(2):112-113. doi:10.1053/ajem.2002.31145

137. Koeijers JJ, Kessels AGH, Nys S, et al. Evaluation of the nitrite and leukocyte esterase activity tests for the diagnosis of acute symptomatic urinary tract infection in men. *Clin Infect Dis*. 2007;45(7):894-896. doi:10.1086/521254

138. Lammers RL, Gibson S, Kovacs D, Sears W, Strachan G. Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. *Ann Emerg Med*. 2001;38(5):505-512. doi:10.1067/mem.2001.119427

139. Leman P. Validity of urinalysis and microscopy for detecting urinary tract infection in the emergency department. *Eur J Emerg Med*. 2002;9(2):141-147. doi:10.1097/00063110-200206000-00008

140. Semeniuk H, Church D. Evaluation of the leukocyte esterase and nitrite urine dipstick screening tests for detection of bacteriuria in women with suspected uncomplicated urinary tract infections. *J Clin Microbiol*. 1999;37(9):3051-3052. doi:10.1128/JCM.37.9.3051-3052.1999

141. Sultana RV, Zalstein S, Cameron P, Campbell D. Dipstick urinalysis and the accuracy of the clinical diagnosis of urinary tract infection. *J Emerg Med*. 2001;20(1):13-19. doi:10.1016/s0736-4679(00)00290-0

142. Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med*. 2013;369(20):1883-1891. doi:10.1056/NEJMoa1302186

143. Males BM, Bartholomew WR, Amsterdam D. Leukocyte esterase-nitrite and bioluminescence assays as urine screens. *J Clin Microbiol*. 1985;22(4):531-534. doi:10.1128/jcm.22.4.531-534.1985

144. Klaassen ILM, de Haas V, van Wijk J a. E, Kaspers GJL, Bijlsma M, Bökenkamp A. Pyuria is absent during urinary tract infections in neutropenic patients. *Pediatr Blood Cancer*. 2011;56(5):868-870. doi:10.1002/pbc.22799

145. Stamm WE. Measurement of pyuria and its relation to bacteriuria. *Am J Med*. 1983;75(1B):53-58. doi:10.1016/0002-9343(83)90073-6

146. Mena Lora AJ, Hua J, Ali M, Krill C, Takhsh E, Bleasdale SC. Changing the culture: impact of a diagnostic stewardship intervention for urine culture testing and CAUTI prevention in an urban safety-net community hospital. *Antimicrob Steward Healthc Epidemiol*. 2024;4(1):e14. doi:10.1017/ash.2024.12

147. Werneburg GT, Rhoads DD. Diagnostic stewardship for urinary tract infection: A snapshot of the expert guidance. *CCJM*. 2022;89(10):581-587. doi:10.3949/ccjm.89a.22008

148. O'Grady NP, Alexander E, Alhazzani W, et al. Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU. *Crit Care Med*. 2023;51(11):1570-1586. doi:10.1097/CCM.0000000000006022

149. Howard-Anderson J, Schwab K, Quinn R, Graber CJ. Choosing Wisely Overnight? Residents' Approach to Fever. *Open Forum Infectious Diseases*. 2017;4(2):ofx080. doi:10.1093/ofid/ofx080

150. Hartley S, Valley S, Kuhn L, et al. INAPPROPRIATE TESTING FOR URINARY TRACT INFECTION IN HOSPITALIZED PATIENTS: AN OPPORTUNITY FOR IMPROVEMENT. *Infect Control Hosp Epidemiol*. 2013;34(11):1204-1207. doi:10.1086/673449

151. Leis JA, Rebick GW, Daneman N, et al. Reducing antimicrobial therapy for asymptomatic bacteriuria among noncatheterized inpatients: a proof-of-concept study. *Clin Infect Dis*. 2014;58(7):980-983. doi:10.1093/cid/ciu010

152. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Arch Intern Med*. 2000;160(5):678-682. doi:10.1001/archinte.160.5.678

153. Shimoni Z, Avdiaev R, Froom P. Urine Cultures in Hospitalized Geriatric Patients Presenting With Fever. *The American Journal of the Medical Sciences*. 2017;353(1):17-21. doi:10.1016/j.amjms.2016.11.001

154. Golob JF, Claridge JA, Sando MJ, et al. Fever and Leukocytosis in Critically Ill Trauma Patients: It's Not the Urine*. *Surgical Infections*. 2008;9(1):49-56. doi:10.1089/sur.2007.023

155. Mozafarihashjin M, Leis JA, Maze Dit Mieusement L, et al. Safety, effectiveness and sustainability of a laboratory intervention to de-adopt culture of midstream urine samples among hospitalized patients. *Infect Control Hosp Epidemiol*. 2021;42(1):43-50. doi:10.1017/ice.2020.385

156. Luu A, Dominguez F, Yeshoua B, et al. Reducing Catheter-associated Urinary Tract Infections via Cost-saving Diagnostic Stewardship. *Clin Infect Dis*. 2021;72(11):e883-e886. doi:10.1093/cid/ciaa1512

157. High KP, Bradley SF, Gravenstein S, et al. Clinical Practice Guideline for the Evaluation of Fever and Infection in Older Adult Residents of Long-Term Care Facilities: 2008 Update by the Infectious Diseases Society of America. *J Am Geriatr Soc*. 2009;57(3):375-394. doi:10.1111/j.1532-5415.2009.02175.x

158. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2011;52(4):e56-e93. doi:10.1093/cid/cir073

159. Tran M, Palmer S, Moore DT, et al. Utility of urine cultures during febrile neutropenia workup in hematopoietic stem cell transplantation recipients without urinary symptoms. *Open Forum Infectious Diseases*. Published online May 3, 2023:ofad236. doi:10.1093/ofid/ofad236

160. Flokas ME, Andreatos N, Alevizakos M, Kalbasi A, Onur P, Mylonakis E. Inappropriate Management of Asymptomatic Patients With Positive Urine Cultures: A Systematic Review and Meta-analysis. *Open Forum Infect Dis*. 2017;4(4):ofx207. doi:10.1093/ofid/ofx207

161. Claeys KC, Blanco N, Morgan DJ, Leekha S, Sullivan KV. Advances and Challenges in the Diagnosis and Treatment of Urinary Tract Infections: the Need for Diagnostic Stewardship. *Curr Infect Dis Rep*. 2019;21(4):11. doi:10.1007/s11908-019-0668-7

162. Henderson JT, Webber EM, Bean SI. Screening for Asymptomatic Bacteriuria in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2019;322(12):1195-1205. doi:10.1001/jama.2019.10060

163. Claeys KC, Johnson MD. Leveraging diagnostic stewardship within antimicrobial stewardship programmes. *Drugs Context*. 2023;12:2022-9-5. doi:10.7573/dic.2022-9-5

164. Rehan Z, Pratt C, Babb K, et al. Modified reporting of positive urine cultures to reduce treatment of asymptomatic bacteriuria in long-term care facilities: a randomized controlled trial. *JAC Antimicrob Resist*. 2022;4(5):dlac109. doi:10.1093/jacamr/dlac109

165. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med*. 1982;307(8):463-468. doi:10.1056/NEJM198208193070802

166. Tullus K. Defining urinary tract infection by bacterial colony counts: a case for less than 100,000 colonies/mL as the threshold. *Pediatr Nephrol*. 2019;34(10):1651-1653. doi:10.1007/s00467-019-04291-x

167. Kass EH. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians*. 1956;69:56-64.

168. Szlachta-McGinn A, Douglass KM, Chung UYR, Jackson NJ, Nickel JC, Ackerman AL. Molecular Diagnostic Methods Versus Conventional Urine Culture for Diagnosis and Treatment of Urinary Tract Infection: A Systematic Review and Meta-analysis. *European Urology Open Science*. 2022;44:113-124. doi:10.1016/j.euros.2022.08.009

169. Hilt EE, McKinley K, Pearce MM, et al. Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder. *J Clin Microbiol*. 2014;52(3):871-876. doi:10.1128/JCM.02876-13

170. Lewis DA, Brown R, Williams J, et al. The human urinary microbiome; bacterial DNA in voided urine of asymptomatic adults. *Front Cell Infect Microbiol*. 2013;3:41. doi:10.3389/fcimb.2013.00041

171. Wolfe AJ, Toh E, Shibata N, et al. Evidence of uncultivated bacteria in the adult female bladder. *J Clin Microbiol*. 2012;50(4):1376-1383. doi:10.1128/JCM.05852-11

172. Hugon P, Dufour JC, Colson P, Fournier PE, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. *Lancet Infect Dis*. 2015;15(10):1211-1219. doi:10.1016/S1473-3099(15)00293-5

173. Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in Understanding the Human Urinary Microbiome and Its Potential Role in Urinary Tract Infection. *mBio*. 2020;11(2):e00218-20. doi:10.1128/mBio.00218-20

174. Yarbrough M, Potter R. Urine Cultures. In: *Clinical Microbiology Procedures Handbook*. 5th ed. ASM Press; 2023.

175. Louie M, Louie L, Simor AE. The role of DNA amplification technology in the diagnosis of infectious diseases. *CMAJ*. 2000;163(3):301-309.

176. Kelly BN. UTI detection by PCR: Improving patient outcomes. *Journal of Mass Spectrometry and Advances in the Clinical Lab*. 2023;28:60-62. doi:10.1016/j.jmsacl.2023.02.006

177. Festa RA, Opel M, Mathur M, et al. Quantitative multiplex polymerase chain reaction in copies ml–1 linearly correlates with standard urine culture in colonies ml−1 for urinary tract infection (UTI) pathogens. *Letters in Applied Microbiology*. 2023;76(8):ovad085. doi:10.1093/lambio/ovad085

178. Wojno KJ, Baunoch D, Luke N, et al. Multiplex PCR Based Urinary Tract Infection (UTI) Analysis Compared to Traditional Urine Culture in Identifying Significant Pathogens in Symptomatic Patients. *Urology*. 2020;136:119-126. doi:10.1016/j.urology.2019.10.018

179. Neuenschwander FR, Groß B, Schubert S. Rapid Antibiotic Susceptibility Testing of Gram-Negative Bacteria Directly from Urine Samples of UTI Patients Using MALDI-TOF MS. *Antibiotics*. 2023;12(6):1042. doi:10.3390/antibiotics12061042

180. Kim Y, Seo MR, Kim SJ, et al. Usefulness of Blood Cultures and Radiologic Imaging Studies in the Management of Patients with Community-Acquired Acute Pyelonephritis. *Infect Chemother*. 2017;49(1):22-30. doi:10.3947/ic.2017.49.1.22

181. Soulen MC, Fishman EK, Goldman SM, Gatewood OM. Bacterial renal infection: role of CT. *Radiology*. 1989;171(3):703-707. doi:10.1148/radiology.171.3.2655002

182. Pierce C, Keniston A, Albert RK. Imaging in Acute Pyelonephritis: Utilization, Findings, and Effect on Management. *South Med J*. 2019;112(2):118-124. doi:10.14423/SMJ.0000000000000936

183. Enikeev DV, Glybochko P, Alyaev Y, Enikeev M, Rapoport L. Imaging technologies in the diagnosis and treatment of acute pyelonephritis. *Urologia*. 2017;84(3):179-184. doi:10.5301/uj.5000234

184. Johnson JR, Russo TA. Acute Pyelonephritis in Adults. *N Engl J Med*. 2018;378(1):48-59. doi:10.1056/nejmcp1702758

185. Faletti R, Cassinis MC, Fonio P, et al. Diffusion-weighted imaging and apparent diffusion coefficient values versus contrast-enhanced MR imaging in the identification and characterisation of acute pyelonephritis. *Eur Radiol*. 2013;23(12):3501-3508. doi:10.1007/s00330-013-2951-6

186. Leyendecker JR, Clingan MJ. Magnetic resonance urography update--are we there yet? *Semin Ultrasound CT MR*. 2009;30(4):246-257. doi:10.1053/j.sult.2009.03.004

187. Craig WD, Wagner BJ, Travis MD. Pyelonephritis: radiologic-pathologic review. *Radiographics*. 2008;28(1):255-277; quiz 327-328. doi:10.1148/rg.281075171

188. Manjunath DrBT, Reddy DrAK, Chikkananjaiah DrSS. Clinico-demographic profile and comparative assessment of ultrasonography and computed tomography examination in the diagnosis of urinary tract infections. *Int J Radiol Diagn Imaging*. 2021;4(1):151-154. doi:10.33545/26644436.2021.v4.i1c.175

189. Mitterberger M, Pinggera GM, Colleselli D, et al. Acute pyelonephritis: comparison of diagnosis with computed tomography and contrast-enhanced ultrasonography. *BJU Int*. 2008;101(3):341-344. doi:10.1111/j.1464-410X.2007.07280.x

190. Yoo JM, Koh JS, Han CH, et al. Diagnosing Acute Pyelonephritis with CT, Tc-DMSA SPECT, and Doppler Ultrasound: A Comparative Study. *Korean J Urol*. 2010;51(4):260-265. doi:10.4111/kju.2010.51.4.260

191. Nikolaidis P, Dogra VS, Goldfarb S, et al. ACR Appropriateness Criteria(®) Acute Pyelonephritis. *J Am Coll Radiol*. 2018;15(11S):S232-S239. doi:10.1016/j.jacr.2018.09.011

192. Abraham G, Reddy YNV, George G. Diagnosis of acute pyelonephritis with recent trends in management. *Nephrol Dial Transplant*. 2012;27(9):3391-3394. doi:10.1093/ndt/gfs327

193. Lee A, Kim HC, Hwang SI, et al. Clinical Usefulness of Unenhanced Computed Tomography in Patients with Acute Pyelonephritis. *J Korean Med Sci*. 2018;33(38):e236. doi:10.3346/jkms.2018.33.e236

194. Bova JG, Potter JL, Arevalos E, Hopens T, Goldstein HM, Radwin HM. Renal and perirenal infection: the role of computerized tomography. *J Urol*. 1985;133(3):375-378. doi:10.1016/s0022-5347(17)48982-8

195. Dalla-Palma L, Pozzi-Mucelli F, Pozzi-Mucelli RS. Delayed CT findings in acute renal infection. *Clin Radiol*. 1995;50(6):364-370. doi:10.1016/s0009-9260(05)83132-0

196. Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis*. 2007;45(3):273-280. doi:10.1086/519268

197. Fontanilla T, Minaya J, Cortés C, et al. Acute complicated pyelonephritis: contrast-enhanced ultrasound. *Abdom Imaging*. 2012;37(4):639-646. doi:10.1007/s00261-011-9781-2

198. Kim B, Lim HK, Choi MH, et al. Detection of parenchymal abnormalities in acute pyelonephritis by pulse inversion harmonic imaging with or without microbubble ultrasonographic contrast agent: correlation with computed tomography. *J Ultrasound Med*. 2001;20(1):5-14. doi:10.7863/jum.2001.20.1.5

199. Rasmussen PE, Nielsen FR. Hydronephrosis during pregnancy: a literature survey. *Eur J Obstet Gynecol Reprod Biol*. 1988;27(3):249-259. doi:10.1016/0028-2243(88)90130-x

200. Venkatesh L, Hanumegowda RK. Acute Pyelonephritis - Correlation of Clinical Parameter with Radiological Imaging Abnormalities. *J Clin Diagn Res*. 2017;11(6):TC15-TC18. doi:10.7860/JCDR/2017/27247.10033

201. Majd M, Nussbaum Blask AR, Markle BM, et al. Acute pyelonephritis: comparison of diagnosis with 99mTc-DMSA, SPECT, spiral CT, MR imaging, and power Doppler US in an experimental pig model. *Radiology*. 2001;218(1):101-108. doi:10.1148/radiology.218.1.r01ja37101

202. El-Ghar MA, Farg H, Sharaf DE, El-Diasty T. CT and MRI in Urinary Tract Infections: A Spectrum of Different Imaging Findings. *Medicina (Kaunas)*. 2021;57(1):32. doi:10.3390/medicina57010032

203. Chua ME, Ming JM, Farhat WA. Magnetic resonance urography in the pediatric population: a clinical perspective. *Pediatr Radiol*. 2016;46(6):791-795. doi:10.1007/s00247-016-3577-z

204. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med*. 2000;160(5):673-677. doi:10.1001/archinte.160.5.673

205. Warren JW, Tenney JH, Hoopes JM, Muncie HL, Anthony WC. A Prospective Microbiologic Study of Bacteriuria in Patients with Chronic Indwelling Urethral Catheters. *The Journal of Infectious Diseases*. 1982;146(6):719-723. doi:10.1093/infdis/146.6.719

206. Abdel-Latif M, Mosbah A, El Bahnasawy MS, Elsawy E, Shaaban AA. Asymptomatic bacteriuria in men with orthotopic ileal neobladders: possible relationship to nocturnal enuresis. *BJU Int*. 2005;96(3):391-396. doi:10.1111/j.1464-410X.2005.05637.x

207. Morris EJ, Bracken RB, Hopfer RL, Mills K, Rodriguez DB. Urinary findings in 20 asymptomatic patients with an ileal conduit. *J Enterostomal Ther*. 1982;9(2):24-27. doi:10.1097/00152192-198203000-00022

208. Schwartz DS, Barone JE. Correlation of urinalysis and dipstick results with catheter-associated urinary tract infections in surgical ICU patients. *Intensive Care Med*. 2006;32(11):1797-1801. doi:10.1007/s00134-006-0365-5

209. Stovall RT, Haenal JB, Jenkins TC, et al. A negative urinalysis rules out catheter-associated urinary tract infection in trauma patients in the intensive care unit. *J Am Coll Surg*. 2013;217(1):162-166. doi:10.1016/j.jamcollsurg.2013.02.030

210. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. *Am J Infect Control*. 2004;32(3):177-183. doi:10.1016/j.ajic.2003.08.005

211. Steward DK, Wood GL, Cohen RL, Smith JW, Mackowiak PA. Failure of the urinalysis and quantitative urine culture in diagnosing symptomatic urinary tract infections in patients with long-term urinary catheters. *Am J Infect Control*. 1985;13(4):154-160. doi:10.1016/0196-6553(85)90102-6

212. Magistro G, Zimmermann L, Bischoff R, et al. The natural course of urinalysis after urinary diversion. *World J Urol*. 2021;39(5):1559-1567. doi:10.1007/s00345-020-03355-0

213. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2010;50(5):625-663. doi:10.1086/650482

214. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. *JAMA*. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627

215. Park DW, Peck KR, Chung MH, et al. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. *J Korean Med Sci*. 2012;27(5):476-483. doi:10.3346/jkms.2012.27.5.476

216. Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. *Clin Infect Dis*. 2021;73(11):1992-1999. doi:10.1093/cid/ciab560

217. Tandogdu Z, Wagenlehner FME. Global epidemiology of urinary tract infections. *Curr Opin Infect Dis*. 2016;29(1):73-79. doi:10.1097/QCO.0000000000000228

218. SUBCOMMITTEE ON URINARY TRACT INFECTION. 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*. 2016;138(6):e20163026. doi:10.1542/peds.2016-3026

219. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, Van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. *Clinical Infectious Diseases*. Published online July 18, 2023:ciad428. doi:10.1093/cid/ciad428

220. Cag Y, Haciseyitoglu D, Ozdemir AA, Cag Y. Antibiotic Resistance and Bacteria in Urinary Tract Infections in Pediatric Patients. *Medeni Med J*. 2021;36(3):217-224. doi:10.5222/MMJ.2021.78535

221. Brosh-Nissimov T, Navon-Venezia S, Keller N, Amit S. Risk analysis of antimicrobial resistance in outpatient urinary tract infections of young healthy adults. *J Antimicrob Chemother*. 2019;74(2):499-502. doi:10.1093/jac/dky424

222. DeMarsh M, Bookstaver PB, Gordon C, et al. Prediction of trimethoprim/sulfamethoxazole resistance in community-onset urinary tract infections. *J Glob Antimicrob Resist*. 2020;21:218-222. doi:10.1016/j.jgar.2019.10.023

223. Hooton TM, Winter C, Tiu F, Stamm WE. Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. *JAMA*. 1995;273(1):41-45.

224. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA*. 2012;307(6):583-589. doi:10.1001/jama.2012.80

225. Watson JR, Burch C, Leber AL. Surrogate testing of oral third-generation cephalosporin susceptibility to common uropathogens. *Diagn Microbiol Infect Dis*. 2021;99(4):115299. doi:10.1016/j.diagmicrobio.2020.115299

226. Schuetz AN, Brasso WB, Crandon JL, et al. Cefazolin as a class representative for oral cephalosporins and uncomplicated urinary tract infections caused by indicated Enterobacteriaceae. *Diagn Microbiol Infect Dis*. 2013;77(4):381-382. doi:10.1016/j.diagmicrobio.2013.08.024

227. Murphy ME, Powell E, Courter J, Mortensen JE. Predicting Oral Beta-lactam susceptibilities against Streptococcus pneumoniae. *BMC Infect Dis*. 2021;21(1):679. doi:10.1186/s12879-021-06341-y

228. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *JAMA*. 2005;293(8):949-955. doi:10.1001/jama.293.8.949

229. Rodríguez-Baño J, Alcalá JC, Cisneros JM, et al. Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Arch Intern Med*. 2008;168(17):1897-1902. doi:10.1001/archinte.168.17.1897

230. Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? *Antimicrob Agents Chemother*. 2019;63(1):e02165-18. doi:10.1128/AAC.02165-18

231. Khan AJ. Efficacy of single-dose therapy of urinary tract infection in infants and children: a review. *J Natl Med Assoc*. 1994;86(9):690-696.

232. Wallen L, Zeller WP, Goessler M, Connor E, Yogev R. Single-dose amikacin treatment of first childhood E. coli lower urinary tract infections. *J Pediatr*. 1983;103(2):316-319. doi:10.1016/s0022-3476(83)80376-x

233. Krzeska I. Amikacin--single dose treatment for uncomplicated urinary tract infections in children. *J Chemother*. 1989;1(4 Suppl):862-863.

234. MR08Ed1E | Cefazolin Breakpoints for Enterobacterales (Uncomplicated Urinary Tract Infections), 1st Edition. Clinical & Laboratory Standards Institute. Accessed March 18, 2024. https://clsi.org/standards/products/microbiology/companion/mr08/

235. Otoom S, Hasan M, Najib N. COMPARATIVE BIOAVAILABILITY OF TWO CEFADROXIL PRODUCTS USING SERUM AND URINE DATA IN HEALTHY HUMAN VOLUNTEERS. *Clin Exp Pharma Physio*. 2004;31(7):433-437. doi:10.1111/j.1440-1681.2004.04012.x

236. Stewart AG, Harris PNA, Henderson A, Schembri MA, Paterson DL. Oral cephalosporin and β-lactamase inhibitor combinations for ESBL-producing Enterobacteriaceae urinary tract infections. *Journal of Antimicrobial Chemotherapy*. 2020;75(9):2384-2393. doi:10.1093/jac/dkaa183

237. Cephalexin Tablets and Oral Suspensions [Package Insert]. Published online May 2018.

238. Khoo KSM, Lim ZY, Chai CY, Mahadevan M, Kuan WS. Management of acute pyelonephritis in the emergency department observation unit. *Singapore Med J*. 2021;62(6):287-295. doi:10.11622/smedj.2020020

239. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA*. 2000;283(12):1583-1590. doi:10.1001/jama.283.12.1583

240. Kaye KS, Rice LB, Dane AL, et al. Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial. *Clin Infect Dis*. 2019;69(12):2045-2056. doi:10.1093/cid/ciz181

241. Chen GJ, Pan SC, Foo J, Morel C, Chen WT, Wang JT. Comparing ceftolozane/tazobactam versus piperacillin/tazobactam as empiric therapy for complicated urinary tract infection in

Taiwan: A cost-utility model focusing on gram-negative bacteria. *J Microbiol Immunol Infect*. 2019;52(5):807-815. doi:10.1016/j.jmii.2019.04.003

242. Dalgic N, Sancar M, Bayraktar B, Dincer E, Pelit S. Ertapenem for the treatment of urinary tract infections caused by extended-spectrum β-lactamase-producing bacteria in children. *Scand J Infect Dis*. 2011;43(5):339-343. doi:10.3109/00365548.2011.553241

243. Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. *J Urol*. 2000;164(4):1254-1258.

244. Jacobsen SM, Stickler DJ, Mobley HLT, Shirtliff ME. Complicated Catheter-Associated Urinary Tract Infections Due to Escherichia coli and Proteus mirabilis. *Clin Microbiol Rev*. 2008;21(1):26-59. doi:10.1128/CMR.00019-07

245. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37(11):1288-1301. doi:10.1017/ice.2016.174

246. Spellberg B, Aggrey G, Brennan MB, et al. Use of Novel Strategies to Develop Guidelines for Management of Pyogenic Osteomyelitis in Adults: A WikiGuidelines Group Consensus Statement. *JAMA Netw Open*. 2022;5(5):e2211321. doi:10.1001/jamanetworkopen.2022.11321

247. Langford BJ, Daneman N, Diong C, et al. Antibiotic Selection and Duration for Catheter-Associated Urinary Tract Infection in Non-Hospitalized Older Adults: A Population-Based Cohort Study. *ASHE*. 2023;3(1):e132. doi:10.1017/ash.2023.176

248. Barbieri E, Bottigliengo D, Tellini M, et al. Development of a Weighted-Incidence Syndromic Combination Antibiogram (WISCA) to guide the choice of the empiric antibiotic treatment for urinary tract infection in paediatric patients: a Bayesian approach. *Antimicrob Resist Infect Control*. 2021;10(1):74. doi:10.1186/s13756-021-00939-2

249. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharm J*. 2018;26(5):678-684. doi:10.1016/j.jsps.2018.02.023

250. Larramendy S, Deglaire V, Dusollier P, et al. Risk Factors of Extended-Spectrum Beta-Lactamases-Producing Escherichia coli Community Acquired Urinary Tract Infections: A Systematic Review. *Infect Drug Resist*. 2020;13:3945-3955. doi:10.2147/IDR.S269033

251. Brown DG, Worby CJ, Pender MA, et al. Development of a prediction model for the acquisition of extended spectrum beta-lactam-resistant organisms in U.S. international travellers. *J Travel Med*. 2023;30(6):taad028. doi:10.1093/jtm/taad028

252. Sperrin M, Riley RD, Collins GS, Martin GP. Targeted validation: validating clinical prediction models in their intended population and setting. *Diagn Progn Res*. 2022;6(1):24. doi:10.1186/s41512-022-00136-8

253. Ben Ayed H, Koubaa M, Hammami F, et al. Performance of an Easy and Simple New Scoring Model in Predicting Multidrug-Resistant Enterobacteriaceae in Community-Acquired Urinary Tract Infections. *Open Forum Infect Dis*. 2019;6(4):ofz103. doi:10.1093/ofid/ofz103

254. Ruiz-Ramos J, Monje-López ÁE, Medina-Catalan D, et al. PREDICTION OF MULTIDRUG-RESISTANT BACTERIA IN URINARY TRACT INFECTIONS IN THE EMERGENCY DEPARTMENT. *J Emerg Med*. 2023;65(1):1-6. doi:10.1016/j.jemermed.2023.04.004

255. Lodise TP, Chen LH, Wei R, et al. Clinical Risk Scores to Predict Nonsusceptibility to Trimethoprim-Sulfamethoxazole, Fluoroquinolone, Nitrofurantoin, and Third-Generation Cephalosporin Among Adult Outpatient Episodes of Complicated Urinary Tract Infection. *Open Forum Infect Dis*. 2023;10(8):ofad319. doi:10.1093/ofid/ofad319

256. Yang J, Eyre DW, Lu L, Clifton DA. Interpretable machine learning-based decision support for prediction of antibiotic resistance for complicated urinary tract infections. *npj Antimicrob Resist*. 2023;1(1):14. doi:10.1038/s44259-023-00015-2

257. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-281. doi:10.1111/j.1469-0691.2011.03570.x

258. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases*. 2018;18(3):318-327. doi:10.1016/S1473-3099(17)30753-3

259. Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in paediatric urinary tract infections: A systematic review and meta-analysis. *J Infect*. 2016;73(6):547-557. doi:10.1016/j.jinf.2016.07.014

260. Butler-Laporte G, Cheng MP, McDonald EG, Lee TC. Using VRE screening tests to predict vancomycin resistance in enterococcal bacteremia. *Infect Control Hosp Epidemiol*. 2020;41(4):425-429. doi:10.1017/ice.2019.380

261. Butler-Laporte G, Cheng MP, Cheng AP, McDonald EG, Lee TC. Using MRSA Screening Tests To Predict Methicillin Resistance in Staphylococcus aureus Bacteremia. *Antimicrob Agents Chemother*. 2016;60(12):7444-7448. doi:10.1128/AAC.01751-16

262. MacFadden DR, Coburn B, Shah N, et al. Utility of prior cultures in predicting antibiotic resistance of bloodstream infections due to Gram-negative pathogens: a multicentre observational cohort study. *Clinical Microbiology and Infection*. 2018;24(5):493-499. doi:10.1016/j.cmi.2017.07.032

263. Pogue JM, Kaye KS, Cohen DA, Marchaim D. Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. *Clinical Microbiology and Infection*. 2015;21(4):302-312. doi:10.1016/j.cmi.2014.12.025

264. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. doi:10.1097/CCM.0000000000005337

265. Langford BJ, Daneman N, Diong C, et al. Antibiotic susceptibility reporting and association with antibiotic prescribing: a cohort study. *Clin Microbiol Infect*. 2021;27(4):568-575. doi:10.1016/j.cmi.2020.10.001

266. Kadry N, Natarajan M, Bein E, Kim P, Farley J. Discordant Clinical and Microbiological Outcomes Are Associated With Late Clinical Relapse in Clinical Trials for Complicated Urinary Tract Infections. *Clin Infect Dis*. 2023;76(10):1768-1775. doi:10.1093/cid/ciad010

267. Zaoutis T, Shaikh N, Fisher BT, et al. Short-Course Therapy for Urinary Tract Infections in Children: The SCOUT Randomized Clinical Trial. *JAMA Pediatr*. 2023;177(8):782-789. doi:10.1001/jamapediatrics.2023.1979

268. Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. *J Antimicrob Chemother*. 2001;48(6):895-901. doi:10.1093/jac/48.6.895

269. Efstathiou SP, Pefanis AV, Tsioulos DI, et al. Acute pyelonephritis in adults: prediction of mortality and failure of treatment. *Arch Intern Med*. 2003;163(10):1206-1212. doi:10.1001/archinte.163.10.1206

270. Pertel PE, Haverstock D. Risk factors for a poor outcome after therapy for acute pyelonephritis. *BJU Int*. 2006;98(1):141-147. doi:10.1111/j.1464-410X.2006.06222.x

271. Karve S, Ryan K, Peeters P, et al. The impact of initial antibiotic treatment failure: Real-world insights in patients with complicated urinary tract infection. *J Infect*. 2018;76(2):121-131. doi:10.1016/j.jinf.2017.11.001

272. Rosa R, Abbo LM, Raney K, Tookes HE 3rd, Supino M. Antimicrobial resistance in urinary tract infections at a large urban ED: Factors contributing to empiric treatment failure. *Am J Emerg Med*. 2017;35(3):397-401. doi:10.1016/j.ajem.2016.11.021

273. Jorgensen S, Zurayk M, Yeung S, et al. Risk factors for early return visits to the emergency department in patients with urinary tract infection. *Am J Emerg Med*. 2018;36(1):12-17. doi:10.1016/j.ajem.2017.06.041

274. Pujades-Rodriguez M, West RM, Wilcox MH, Sandoe J. Lower Urinary Tract Infections: Management, Outcomes and Risk Factors for Antibiotic Re-prescription in Primary Care. *EClinicalMedicine*. 2019;14:23-31. doi:10.1016/j.eclinm.2019.07.012

275. Eliakim-Raz N, Babitch T, Shaw E, et al. Risk Factors for Treatment Failure and Mortality Among Hospitalized Patients With Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group). *Clin Infect Dis*. 2019;68(1):29-36. doi:10.1093/cid/ciy418

276. Martischang R, Godycki-Ćwirko M, Kowalczyk A, et al. Risk factors for treatment failure in women with uncomplicated lower urinary tract infection. *PLoS One*. 2021;16(8):e0256464. doi:10.1371/journal.pone.0256464

277. Trautner BW, Kaye KS, Gupta V, et al. Risk Factors Associated With Antimicrobial Resistance and Adverse Short-Term Health Outcomes Among Adult and Adolescent Female Outpatients With Uncomplicated Urinary Tract Infection. *Open Forum Infect Dis*. 2022;9(12):ofac623. doi:10.1093/ofid/ofac623

278. Dunne MW, Puttagunta S, Aronin SI, Brossette S, Murray J, Gupta V. Impact of Empirical Antibiotic Therapy on Outcomes of Outpatient Urinary Tract Infection Due to Nonsusceptible Enterobacterales. *Microbiol Spectr*. 2022;10(1):e0235921. doi:10.1128/spectrum.02359-21

279. Lamas Ferreiro JL, Álvarez Otero J, González González L, et al. Pseudomonas aeruginosa urinary tract infections in hospitalized patients: Mortality and prognostic factors. *PLoS One*. 2017;12(5):e0178178. doi:10.1371/journal.pone.0178178

280. Siddiqui H, Nederbragt AJ, Lagesen K, Jeansson SL, Jakobsen KS. Assessing diversity of the female urine microbiota by high throughput sequencing of 16S rDNA amplicons. *BMC Microbiol*. 2011;11:244. doi:10.1186/1471-2180-11-244

281. Adu-Oppong B, Thänert R, Wallace MA, Burnham CAD, Dantas G. Substantial overlap between symptomatic and asymptomatic genitourinary microbiota states. *Microbiome*. 2022;10:6. doi:10.1186/s40168-021-01204-9

282. Aragón IM, Herrera-Imbroda B, Queipo-Ortuño MI, et al. The Urinary Tract Microbiome in Health and Disease. *Eur Urol Focus*. 2018;4(1):128-138. doi:10.1016/j.euf.2016.11.001

283. Siddiqui H, Lagesen K, Nederbragt AJ, Jeansson SL, Jakobsen KS. Alterations of microbiota in urine from women with interstitial cystitis. *BMC Microbiol*. 2012;12:205. doi:10.1186/1471-2180-12-205

284. Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract--a role beyond infection. *Nat Rev Urol*. 2015;12(2):81-90. doi:10.1038/nrurol.2014.361

285. Neugent ML, Kumar A, Hulyalkar NV, et al. Recurrent urinary tract infection and estrogen shape the taxonomic ecology and function of the postmenopausal urogenital microbiome. *Cell Rep Med*. 2022;3(10):100753. doi:10.1016/j.xcrm.2022.100753

286. Ljubetic BM, Mohammad A, Durrani B, Dobberfuhl AD. Pathophysiologic Insights into the Transition from Asymptomatic Bacteriuria to Urinary Tract Infection. *Curr Urol Rep*. 2023;24(11):533-540. doi:10.1007/s11934-023-01183-4

287. Moustafa A, Li W, Singh H, et al. Microbial metagenome of urinary tract infection. *Sci Rep*. 2018;8:4333. doi:10.1038/s41598-018-22660-8

288. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. *Cochrane Database Syst Rev*. 2008;(3):CD001535. doi:10.1002/14651858.CD001535.pub2

289. Rosa R, Abbo LM, Raney K, Tookes HE, Supino M. Antimicrobial resistance in urinary tract infections at a large urban ED: Factors contributing to empiric treatment failure. *Am J Emerg Med*. 2017;35(3):397-401. doi:10.1016/j.ajem.2016.11.021

290. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. *Cochrane Database Syst Rev*. 2003;(1):CD003966. doi:10.1002/14651858.CD003966

291. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. *Cochrane Database Syst Rev*. 2012;(8):CD006857. doi:10.1002/14651858.CD006857.pub2

292. Moreira MVB, de Freitas LR, Fonseca LM, et al. Shorter versus longer-course of antibiotic therapy for urinary tract infections in pediatric population: an updated meta-analysis. *Eur J Pediatr*. 2024;183(5):2037-2047. doi:10.1007/s00431-024-05512-8

293. Rocca Rossetti S. Single-shot vs conventional therapy with amikacin for treatment of uncomplicated urinary tract infections: a multicenter study. *Chemioterapia*. 1986;5(6):394-399.

294. Caramalli S, Amprimo MC, Cavalli G, et al. Effect and pharmacokinetics of netilmicin given as bolus intramuscular administration: an open comparative trial versus amikacin and fosfomycin in elderly patients affected by urinary tract infections. *Int J Clin Pharmacol Res*. 1991;11(2):55-65.

295. Bailey RR, Abbott GD. Treatment of urinary-tract infection with a single dose of amoxycillin. *Nephron*. 1977;18(6):316-320. doi:10.1159/000180849

296. Stahl GE, Topf P, Fleisher GR, Norman ME, Rosenblum HW, Gruskin AB. Single-dose treatment of uncomplicated urinary tract infections in children. *Ann Emerg Med*. 1984;13(9 Pt 1):705-708. doi:10.1016/s0196-0644(84)80732-5

297. Fine JS, Jacobson MS. Single-dose versus conventional therapy of urinary tract infections in female adolescents. *Pediatrics*. 1985;75(5):916-920.

298. Shapiro ED, Wald ER. Single-dose amoxicillin treatment of urinary tract infections. *J Pediatr*. 1981;99(6):989-992. doi:10.1016/s0022-3476(81)80039-x

299. Pitt WR, Dyer SA, McNee JL, Burke JR. Single dose trimethoprim-sulphamethoxazole treatment of symptomatic urinary infection. *Arch Dis Child*. 1982;57(3):229-231. doi:10.1136/adc.57.3.229

300. Avner ED, Ingelfinger JR, Herrin JT, et al. Single-dose amoxicillin therapy of uncomplicated pediatric urinary tract infections. *J Pediatr*. 1983;102(4):623-627. doi:10.1016/s0022-3476(83)80207-8

301. Madrigal G, Odio CM, Mohs E, Guevara J, McCracken GHJ. Single dose antibiotic therapy is not as effective as conventional regimens for management of acute urinary tract infections in children. *Pediatr Infect Dis J*. 1988;7(5):316-319. doi:10.1097/00006454-198805000-00004

302. Keren R, Chan E. A meta-analysis of randomized, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children. *Pediatrics*. 2002;109(5):E70-70. doi:10.1542/peds.109.5.e70

303. Helin I. Three-day therapy with cephalexin for lower urinary tract infections in children. *Scand J Infect Dis*. 1984;16(3):305-307. doi:10.3109/00365548409070405

304. Khan AJ, Kumar K, Evans HE. Three-day antimicrobial therapy of urinary tract infection. *J Pediatr*. 1981;99(6):992-994. doi:10.1016/s0022-3476(81)80040-6

305. McCracken GHJ, Ginsburg CM, Namasonthi V, Petruska M. Evaluation of short-term antibiotic therapy in children with uncomplicated urinary tract infections. *Pediatrics*. 1981;67(6):796-801.

306. Tambic T, Oberiter V, Delmis J, Tambic A. Diagnostic value of a P-fimbriation test in determining duration of therapy in children with urinary tract infections. *Clin Ther*. 1992;14(5):667-671.

307. Kornberg AE, Sherin K, Veiga P, Mydlow PK, Collins JJ, Feld LG. Two-day therapy with cefuroxime axetil is effective for urinary tract infections in children. *Am J Nephrol*. 1994;14(3):169-172. doi:10.1159/000168709

308. Short-term treatment of acute urinary tract infection in girls. Copenhagen Study Group of Urinary Tract Infections in Children. *Scand J Infect Dis*. 1991;23(2):213-220. doi:10.3109/00365549109023403

309. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy*. 2013;68(10):2183-2191. doi:10.1093/jac/dkt177

310. Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Kidney and Transplant Group, ed. *Cochrane Database of Systematic Reviews*. 2014;2014(7). doi:10.1002/14651858.CD003772.pub4

311. Montini G, Tessitore A, Console K, et al. Short Oral Antibiotic Therapy for Pediatric Febrile Urinary Tract Infections: A Randomized Trial. *Pediatrics*. 2024;153(1):e2023062598. doi:10.1542/peds.2023-062598

312. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. *JAMA Netw Open*. 2020;3(5):e203951. doi:10.1001/jamanetworkopen.2020.3951

313. Afolabi TM, Goodlet KJ, Fairman KA. Association of Antibiotic Treatment Duration With Recurrence of Uncomplicated Urinary Tract Infection in Pediatric Patients. *Ann Pharmacother*. 2020;54(8):757-766. doi:10.1177/1060028019900650

314. Montini G, Toffolo A, Zucchetta P, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *BMJ*. 2007;335(7616):386. doi:10.1136/bmj.39244.692442.55

315. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1 Pt 1):79-86. doi:10.1542/peds.104.1.79

316. Bocquet N, Sergent Alaoui A, Jais JP, et al. Randomized trial of oral versus sequential IV/oral antibiotic for acute pyelonephritis in children. *Pediatrics*. 2012;129(2):e269-275. doi:10.1542/peds.2011-0814

317. Neuhaus TJ, Berger C, Buechner K, et al. Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. *Eur J Pediatr*. 2008;167(9):1037-1047. doi:10.1007/s00431-007-0638-1

318. Benador D, Neuhaus TJ, Papazyan JP, 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):241-246. doi:10.1136/adc.84.3.241

319. Bouissou F, Munzer C, Decramer S, 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):e553-560. doi:10.1542/peds.2006-3632

320. Francois P, Bensman A, Begue P, Artaz MA, Coudeville L, Lebrun T. 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;27:667-673.

321. 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):1513-1515.

322. Vilaichone A, Watana D, Chaiwatanarat T. Oral ceftibuten switch therapy for acute pyelonephritis in children. *J Med Assoc Thai*. 2001;84 Suppl 1:S61-67.

323. 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):878-884. doi:10.1007/s004670100690

324. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother*. 2015;70(9):2456-2464. doi:10.1093/jac/dkv147

325. Kim DK, Kim JH, Lee JY, 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 trials. *The Lancet Infectious Diseases*. 2020;20(9):1080-1088. doi:10.1016/S1473-3099(20)30121-3

326. 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(482):729-734.

327. Trienekens TA, Stobberingh EE, Winkens RA, Houben AW. Different lengths of treatment with co-trimoxazole for acute uncomplicated urinary tract infections in women. *BMJ*. 1989;299(6711):1319-1322. doi:10.1136/bmj.299.6711.1319

328. Gossius G, Vorland L. A randomised comparison of single-dose vs. three-day and ten-day therapy with trimethoprim-sulfamethoxazole for acute cystitis in women. *Scand J Infect Dis*. 1984;16(4):373-379. doi:10.3109/00365548409073963

329. Hooton TM, Latham RH, Wong ES, Johnson C, Roberts PL, Stamm WE. Ofloxacin versus trimethoprim-sulfamethoxazole for treatment of acute cystitis. *Antimicrobial Agents and Chemotherapy*. 1989;33(8):1308-1312. doi:10.1128/aac.33.8.1308

330. Neringer R, Forsgren A, Hansson C, Ode B. Lomefloxacin versus norfloxacin in the treatment of uncomplicated urinary tract infections: three-day versus seven-day treatment. The South Swedish Lolex Study Group. *Scand J Infect Dis*. 1992;24(6):773-780. doi:10.3109/00365549209062463

331. Trienekens TA, London NH, Houben AW, De Jong RA, Stobberingh EE. Treating acute urinary tract infections. An RCT of 3-day versus 7-day norfloxacin. *Can Fam Physician*. 1993;39:514-518.

332. Arredondo-García JL, Figueroa-Damián R, Rosas A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *J Antimicrob Chemother*. 2004;54(4):840-843. doi:10.1093/jac/dkh414

333. Vogel T, Verreault R, Gourdeau M, Morin M, Grenier-Gosselin L, Rochette L. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. *CMAJ*. 2004;170(4):469-473.

334. Bahman H, Hyaide O, Omid N, et al. Comparison of 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated urinary tract infection in women: a randomized double-blind clinical trial. Published online 2010:70-74.

335. Boerema JB, Willems FT. Fosfomycin trometamol in a single dose versus norfloxacin for seven days in the treatment of uncomplicated urinary infections in general practice. *Infection*. 1990;18 Suppl 2:S80-88. doi:10.1007/BF01643433

336. Crocchiolo P. Single-dose fosfomycin trometamol versus multiple-dose cotrimoxazole in the treatment of lower urinary tract infections in general practice. Multicenter Group of General Practitioners. *Chemotherapy*. 1990;36 Suppl 1:37-40. doi:10.1159/000238815

337. Selvaggi FP, Ditonno P, Traficante A, Battaglia M, Di Lorenzo V. Fosfomycin trometamol (Monuril) versus norfloxacin in single dose for adult female uncomplicated UTIs. Multicenter randomized, double-blind study. *Chemotherapy*. 1990;36 Suppl 1:31-33. doi:10.1159/000238813

338. Naber KG, Thyroff-Friesinger U. Fosfomycin trometamol versus ofloxacin/co-trimoxazole as single dose therapy of acute uncomplicated urinary tract infection in females: a multicentre study. *Infection*. 1990;18 Suppl 2:S70-76. doi:10.1007/BF01643431

339. de Jong Z, Pontonnier F, Plante P. Single-dose fosfomycin trometamol (Monuril) versus multiple-dose norfloxacin: results of a multicenter study in females with uncomplicated lower urinary tract infections. *Urol Int*. 1991;46(4):344-348. doi:10.1159/000282164

340. Van Pienbroek E, Hermans J, Kaptein AA, Mulder JD. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharm World Sci*. 1993;15(6):257-262. doi:10.1007/BF01871127

341. Elhanan G, Tabenkin H, Yahalom R, Raz R. Single-dose fosfomycin trometamol versus 5-day cephalexin regimen for treatment of uncomplicated lower urinary tract infections in women. *Antimicrob Agents Chemother*. 1994;38(11):2612-2614. doi:10.1128/AAC.38.11.2612

342. Minassian MA, Lewis DA, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. *Int J Antimicrob Agents*. 1998;10(1):39-47. doi:10.1016/s0924-8579(98)00021-1

343. Ceran N, Mert D, Kocdogan FY, et al. A randomized comparative study of single-dose fosfomycin and 5-day ciprofloxacin in female patients with uncomplicated lower urinary tract infections. *J Infect Chemother*. 2010;16(6):424-430. doi:10.1007/s10156-010-0079-z

344. PIVYA [package insert]. Published online April 30, 2024. Accessed May 25, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216483s000lbl.pdf

345. Richards HH. Comparative efficacy of 3-day and 7-day chemotherapy with twice-daily pivmecillinam in urinary tract infections seen in general practice. *Curr Med Res Opin*. 1984;9(3):197-203. doi:10.1185/03007998409109580

346. Pitkäjärvi T, Pyykönen ML, Kannisto K, Piippo T, Viita P. Pivmecillinam treatment in acute cystitis. Three versus seven days study. *Arzneimittelforschung*. 1990;40(10):1156-1158.

347. 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(1):49-57. doi:10.1080/02813430601183074

348. Jansåker F, Thønnings S, Hertz FB, et al. Three versus five days of pivmecillinam for community-acquired uncomplicated lower urinary tract infection: A randomised, double-blind, placebo-controlled superiority trial. *EClinicalMedicine*. 2019;12:62-69. doi:10.1016/j.eclinm.2019.06.009

349. Wagenlehner F, Perry CR, Hooton TM, et al. Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials. *Lancet*. 2024;403(10428):741-755. doi:10.1016/S0140-6736(23)02196-7

350. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*. 2007;167(20):2207-2212. doi:10.1001/archinte.167.20.2207

351. Van Pienbroek E, Hermans J, Kaptein AA, Mulder JD. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharm World Sci*. 1993;15(6):257-262. doi:10.1007/BF01871127

352. Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother*. 1994;33 Suppl A:121-129. doi:10.1093/jac/33.suppl_a.121

353. Iravani A, Klimberg I, Briefer C, Munera C, Kowalsky SF, Echols RM. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother*. 1999;43 Suppl A:67-75.

354. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clin Ther*. 1999;21(11):1864-1872. doi:10.1016/S0149-2918(00)86734-X

355. Ernst EJ, Ernst ME, Hoehns JD, Bergus GR. Women's quality of life is decreased by acute cystitis and antibiotic adverse effects associated with treatment. *Health Qual Life Outcomes*. 2005;3:45. doi:10.1186/1477-7525-3-45

356. Greenberg RN, Reilly PM, Luppen KL, Weinandt WJ, Ellington LL, Bollinger MR. Randomized study of single-dose, three-day, and seven-day treatment of cystitis in women. *J Infect Dis*. 1986;153(2):277-282. doi:10.1093/infdis/153.2.277

357. Asbach HW. Single dose oral administration of cefixime 400mg in the treatment of acute uncomplicated cystitis and gonorrhoea. *Drugs*. 1991;42 Suppl 4:10-13. doi:10.2165/00003495-199100424-00005

358. Raz R, Rottensterich E, Boger S, Potasman I. Comparison of single-dose administration and three-day course of amoxicillin with those of clavulanic acid for treatment of uncomplicated urinary tract infection in women. *Antimicrob Agents Chemother*. 1991;35(8):1688-1690. doi:10.1128/AAC.35.8.1688

359. Masterton RG, Bochsler JA. High-dosage co-amoxiclav in a single dose versus 7 days of co-trimoxazole as treatment of uncomplicated lower urinary tract infection in women. *Journal of Antimicrobial Chemotherapy*. 1995;35(1):129-137. doi:10.1093/jac/35.1.129

360. Sandberg T, Henning C, Iwarson S, Paulsen O. Cefadroxil once daily for three or seven days versus amoxycillin for seven days in uncomplicated urinary tract infections in women. *Scand J Infect Dis*. 1985;17(1):83-87. doi:10.3109/00365548509070425

361. Raz R, Rottensterich E, Leshem Y, Tabenkin H. Double-blind study comparing 3-day regimens of cefixime and ofloxacin in treatment of uncomplicated urinary tract infections in women. *Antimicrob Agents Chemother*. 1994;38(5):1176-1177. doi:10.1128/AAC.38.5.1176

362. Goto T, Kitagawa T, Kawahara M, Hayami H, Ohi Y. Comparative study of single-dose and three-day therapy for acute uncomplicated cystitis. *Hinyokika Kiyo*. 1999;45(2):85-89.

363. Kavatha D, Giamarellou H, Alexiou Z, et al. Cefpodoxime-proxetil versus trimethoprim-sulfamethoxazole for short-term therapy of uncomplicated acute cystitis in women. *Antimicrob Agents Chemother*. 2003;47(3):897-900. doi:10.1128/AAC.47.3.897-900.2003

364. Hamasuna R, Tanaka K, Hayami H, et al. Treatment of acute uncomplicated cystitis with faropenem for 3 days versus 7 days: multicentre, randomized, open-label, controlled trial. *J Antimicrob Chemother*. 2014;69(6):1675-1680. doi:10.1093/jac/dku014

365. Sadahira T, Wada K, Araki M, et al. Efficacy and safety of 3 day versus 7 day cefditoren pivoxil regimens for acute uncomplicated cystitis: multicentre, randomized, open-label trial. *J Antimicrob Chemother*. 2017;72(2):529-534. doi:10.1093/jac/dkw424

366. Elajouz B, Dumkow LE, Worden LJ, VanLangen KM, Jameson AP. Three-day ceftriaxone versus longer durations of therapy for inpatient treatment of uncomplicated urinary tract infection. *Antimicrob Steward Healthc Epidemiol*. 2022;2(1):e171. doi:10.1017/ash.2022.317

367. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother*. 2000;46 Suppl 1:35-39; discussion 63-65.

368. Nicolle LE, Madsen KS, Debeeck GO, et al. Three days of pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection in women. *Scand J Infect Dis*. 2002;34(7):487-492. doi:10.1080/00365540110080728

369. Vik I, Bollestad M, Grude N, 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. doi:10.1371/journal.pmed.1002569

370. Menday AP. Comparison of pivmecillinam and cephalexin in acute uncomplicated urinary tract infection. *Int J Antimicrob Agents*. 2000;13(3):183-187. doi:10.1016/s0924-8579(99)00118-1

371. Marsh BT, Menday AP. Comparative efficacy of 3-day and 7-day chemotherapy with pivmecillinam in urinary tract infections in general practice. *J Int Med Res*. 1980;8(2):105-111. doi:10.1177/030006058000800201

372. Sutlieff PA. A comparison between a 3-day and a 5-day course of pivmecillinam as a treatment for acute lower urinary tract infections in general practice. *Current Medical Research and Opinion*. 1982;7(9):563-568. doi:10.1185/03007998209110100

373. Hovelius B, Mårdh PA, Nygaard-Pedersen L, Wathne B. Nalidixic acid and pivmecillinam for treatment of acute lower urinary tract infections. *Scand J Prim Health Care*. 1985;3(4):227-232. doi:10.3109/02813438509013954

374. Jansåker F, Boel JB, Thønnings S, et al. Pivmecillinam compared to other antimicrobials for community-acquired urinary tract infections with Escherichia coli, ESBL-producing or not - a retrospective cohort study. *Infect Drug Resist*. 2019;12:1691-1702. doi:10.2147/IDR.S209255

375. Pinart M, Kranz J, Jensen K, et al. Optimal dosage and duration of pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis. *International Journal of Infectious Diseases*. 2017;58:96-109. doi:10.1016/j.ijid.2017.03.012

376. Trienekens TA, Stobberingh EE, Winkens RA, Houben AW. Different lengths of treatment with co-trimoxazole for acute uncomplicated urinary tract infections in women. *BMJ*. 1989;299(6711):1319-1322. doi:10.1136/bmj.299.6711.1319

377. Block JM, Walstad RA, Bjertnaes A, et al. Ofloxacin versus trimethoprim-sulphamethoxazole in acute cystitis. *Drugs*. 1987;34 Suppl 1:100-106. doi:10.2165/00003495-198700341-00022

378. McCarty JM, Richard G, Huck W, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. *Am J Med*. 1999;106(3):292-299. doi:10.1016/s0002-9343(99)00026-1

379. Double-blind comparison of 3-day versus 7-day treatment with norfloxacin in symptomatic urinary tract infections. The Inter-Nordic Urinary Tract Infection Study Group. *Scand J Infect Dis*. 1988;20(6):619-624. doi:10.3109/00365548809035662

380. van Balen FA, Touw-Otten FW, de Melker RA. Single-dose pefloxacin versus five-days treatment with norfloxacin in uncomplicated cystitis in women. *J Antimicrob Chemother*. 1990;26 Suppl B:153-160. doi:10.1093/jac/26.suppl_b.153

381. Hooton TM, Johnson C, Winter C, et al. Single-dose and three-day regimens of ofloxacin versus trimethoprim-sulfamethoxazole for acute cystitis in women. *Antimicrob Agents Chemother*. 1991;35(7):1479-1483. doi:10.1128/AAC.35.7.1479

382. Saginur R, Nicolle LE. Single-dose compared with 3-day norfloxacin treatment of uncomplicated urinary tract infection in women. Canadian Infectious Diseases Society Clinical Trials Study Group. *Arch Intern Med*. 1992;152(6):1233-1237.

383. Iravani A. Multicenter study of single-dose and multiple-dose fleroxacin versus ciprofloxacin in the treatment of uncomplicated urinary tract infections. *Am J Med*. 1993;94(3A):89S-96S.

384. Del Río G, Dalet F, Aguilar L, Caffaratti J, Dal-Ré R. Single-dose rufloxacin versus 3-day norfloxacin treatment of uncomplicated cystitis: clinical evaluation and pharmacodynamic considerations. *Antimicrob Agents Chemother*. 1996;40(2):408-412. doi:10.1128/AAC.40.2.408

385. Auquer F, Cordón F, Gorina E, Caballero JC, Adalid C, Batlle J. Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. *Clin Microbiol Infect*. 2002;8(1):50-54.

386. Richard GA, Mathew CP, Kirstein JM, Orchard D, Yang JY. Single-dose fluoroquinolone therapy of acute uncomplicated urinary tract infection in women: results from a randomized, double-blind, multicenter trial comparing single-dose to 3-day fluoroquinolone regimens. *Urology*. 2002;59(3):334-339. doi:10.1016/s0090-4295(01)01562-x

387. Naber KG, Bartnicki A, Bischoff W, et al. Gatifloxacin 200 mg or 400 mg once daily is as effective as ciprofloxacin 500 mg twice daily for the treatment of patients with acute pyelonephritis or complicated urinary tract infections. *Int J Antimicrob Agents*. 2004;23 Suppl 1:S41-53. doi:10.1016/j.ijantimicag.2003.09.002

388. Stein GE, Philip E. Comparison of three-day temafloxacin with seven-day ciprofloxacin treatment of urinary tract infections in women. *J Fam Pract*. 1992;34(2):180-184.

389. Henry D, Ellison W, Sullivan J, et al. Treatment of community-acquired acute uncomplicated urinary tract infection with sparfloxacin versus ofloxacin. The Sparfloxacin Multi Center UUTI Study Group. *Antimicrob Agents Chemother*. 1998;42(9):2262-2266. doi:10.1128/AAC.42.9.2262

390. Henry DC, Nenad RC, Iravani A, et al. Comparison of sparfloxacin and ciprofloxacin in the treatment of community-acquired acute uncomplicated urinary tract infection in women. Sparfloxacin Multicenter Uncomplicated Urinary Tract Infection Study Group. *Clin Ther*. 1999;21(6):966-981. doi:10.1016/s0149-2918(99)80018-6

391. Richard GA, DeAbate CA, Ruoff GE, Corrado M, Fowler CL, Morgan N. A Double-Blind, Randomized Trial of the Efficacy and Safety of Short-Course, Once-Daily Levofloxacin Versus Ofloxacin Twice Daily in Uncomplicated Urinary Tract Infections. *Infectious Diseases in Clinical Practice*. 2000;9(8):323.

392. Cervigni M, Orticelli G, Bologna M, et al. SINGLE-DOSE PRULIFLOXACIN VERSUS SINGLE-DOSE PEFLOXACIN IN THE TREATMENT OF ACUTE UNCOMPLICATED URINARY TRACT INFECTION IN WOMEN. *Urogynaecologia*. 2003;17(2):69-78. doi:10.4081/uij.2003.69

393. Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. *Clin J Am Soc Nephrol*. 2006;1(2):327-331. doi:10.2215/CJN.01931105

394. Stapleton AE, Wagenlehner FME, Mulgirigama A, Twynholm M. Escherichia coli Resistance to Fluoroquinolones in Community-Acquired Uncomplicated Urinary Tract Infection in Women: a Systematic Review. *Antimicrob Agents Chemother*. 2020;64(10). doi:10.1128/AAC.00862-20

395. Faine BA, Rech MA, Vakkalanka P, et al. High prevalence of fluoroquinolone-resistant UTI among US emergency department patients diagnosed with urinary tract infection, 2018-2020. *Acad Emerg Med*. 2022;29(9):1096-1105. doi:10.1111/acem.14545

396. Anwar AI, Lu L, Plaisance CJ, et al. Fluoroquinolones: Neurological Complications and Side Effects in Clinical Practice. *Cureus*. 16(2):e54565. doi:10.7759/cureus.54565

397. Rusu A, Munteanu AC, Arbănași EM, Uivarosi V. Overview of Side-Effects of Antibacterial Fluoroquinolones: New Drugs versus Old Drugs, a Step Forward in the Safety Profile? *Pharmaceutics*. 2023;15(3):804. doi:10.3390/pharmaceutics15030804

398. Hussen NHA, Qadir SH, Rahman HS, Hamalaw YY, Kareem PSS, Hamza BA. Long-term toxicity of fluoroquinolones: a comprehensive review. *Drug and Chemical Toxicology*. 2023;0(0):1-12. doi:10.1080/01480545.2023.2240036

399. López-Medrano F, Silva JT, Fernández-Ruiz M, et al. Oral fosfomycin for the treatment of lower urinary tract infections among kidney transplant recipients-Results of a Spanish multicenter cohort. *Am J Transplant*. 2020;20(2):451-462. doi:10.1111/ajt.15614

400. Ten Doesschate T, van Werkhoven H, Meijvis S, et al. Fosfomycin-trometamol for Urinary Tract Infections in Kidney Transplant Recipients. *Transplantation*. 2019;103(6):1272-1276. doi:10.1097/TP.0000000000002427

401. Bailey RR, Blake E, Peddie BA. Comparison of single dose netilmicin with a five-day course of co-trimoxazole for uncomplicated urinary tract infections. *N Z Med J*. 1984;97(754):262-264.

402. Prát V, Horcicková M, Hatala M, et al. Single-dose treatment with netilmicin for different clinical forms of urinary tract infections. *Infection*. 1984;12(2):99-101. doi:10.1007/BF01641681

403. Jenrette JE, Coronato K, Miller MA, Molina KC, Quinones A, Jacknin G. Prospective evaluation of single-dose aminoglycosides for treatment of complicated cystitis in the emergency department. *Acad Emerg Med*. Published online March 7, 2024. doi:10.1111/acem.14886

404. Dinh A, Davido B, Etienne M, et al. Is 5 days of oral fluoroquinolone enough for acute uncomplicated pyelonephritis? The DTP randomized trial. *Eur J Clin Microbiol Infect Dis*. 2017;36(8):1443-1448. doi:10.1007/s10096-017-2951-6

405. 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(9840):484-490. doi:10.1016/S0140-6736(12)60608-4

406. Ode B, Bröms M, Walder M, Cronberg S. Failure of excessive doses of ampicillin to prevent bacterial relapse in the treatment of acute pyelonephritis. *Acta Med Scand*. 1980;207(4):305-307. doi:10.1111/j.0954-6820.1980.tb09725.x

407. Jernelius H, Zbornik J, Bauer CA. One or three weeks' treatment of acute pyelonephritis? A double-blind comparison, using a fixed combination of pivampicillin plus pivmecillinam. *Acta Med Scand*. 1988;223(5):469-477. doi:10.1111/j.0954-6820.1988.tb15899.x

408. Mensa J, Moreno-Martinez A, Martinez J. Treatment of acute uncomplicated pyelonephritis (AUP): a randomized trial comparing 7- vs. 14-day therapy. Abstract 613, p. 665 presented at: merican Society for Microbiology Abstracts of the Thirty-ninth Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999; San Francisco, CA.

409. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet*. 2015;385(9981):1949-1956. doi:10.1016/S0140-6736(14)62220-0

410. Bennett WM, Craven R. Urinary Tract Infections in Patients With Severe Renal Disease: Treatment With Ampicillin and Trimethoprim—Sulfamethoxazole. *JAMA*. 1976;236(8):946-948. doi:10.1001/jama.1976.03270090040026

411. 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(3):341-345. doi:10.7326/0003-4819-106-3-341

412. Johnson JR, Lyons MF, Pearce W, et al. Therapy for women hospitalized with acute pyelonephritis: a randomized trial of ampicillin versus trimethoprim-sulfamethoxazole for 14 days. *J Infect Dis*. 1991;163(2):325-330. doi:10.1093/infdis/163.2.325

413. Mouton Y, Ajana F, Chidiac C, Capron MH, Home P, Masquelier AM. A multicenter study of lomefloxacin and trimethoprim/sulfamethoxazole in the treatment of uncomplicated acute pyelonephritis. *The American Journal of Medicine*. 1992;92(4, Supplement 1):S87-S90. doi:10.1016/0002-9343(92)90316-4

414. Yahav D, Franceschini E, Koppel F, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. *Clin Infect Dis*. 2019;69(7):1091-1098. doi:10.1093/cid/ciy1054

415. Molina J, Montero-Mateos E, Praena-Segovia J, et al. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. *Clin Microbiol Infect*. 2022;28(4):550-557. doi:10.1016/j.cmi.2021.09.001

416. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. *JAMA*. 2020;323(21):2160-2169. doi:10.1001/jama.2020.6348

417. Carrie AG, Metge CJ, Collins DM, Harding GKM, Zhanel GG. Use of administrative healthcare claims to examine the effectiveness of trimethoprim-sulfamethoxazole versus fluoroquinolones in the treatment of community-acquired acute pyelonephritis in women. *J Antimicrob Chemother*. 2004;53(3):512-517. doi:10.1093/jac/dkh100

418. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of Trimethoprim-Sulfamethoxazole May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. *Am J Med*. 2017;130(7):842-845. doi:10.1016/j.amjmed.2017.01.025

419. Fosse PE, Brinkman KM, Brink HM, Conner CE, Aden JK, Giancola SE. Comparing outcomes among outpatients treated for pyelonephritis with oral cephalosporins versus first-line agents. *Int J Antimicrob Agents*. 2022;59(4):106560. doi:10.1016/j.ijantimicag.2022.106560

420. de Gier R, Karperien A, Bouter K, et al. A sequential study of intravenous and oral Fleroxacin for 7 or 14 days in the treatment of complicated urinary tract infections. *Int J Antimicrob Agents*. 1995;6(1):27-30. doi:10.1016/0924-8579(95)00011-v

421. Hyslop DL, Bischoff W. Loracarbef (LY163892) versus cefaclor and norfloxacin in the treatment of uncomplicated pyelonephritis. *Am J Med*. 1992;92(6A):86S-94S. doi:10.1016/0002-9343(92)90614-h

422. Sanchez M, Collvinent B, Miró O, et al. Short-term effectiveness of ceftriaxone single dose in the initial treatment of acute uncomplicated pyelonephritis in women. A randomised controlled trial. *Emerg Med J*. 2002;19(1):19-22. doi:10.1136/emj.19.1.19

423. Wagenlehner FME, Ballarini S, Pilatz A, Weidner W, Lehr L, Naber KG. A Randomized, Double-Blind, Parallel-Group, Multicenter Clinical Study of Escherichia coli-Lyophilized Lysate for the Prophylaxis of Recurrent Uncomplicated Urinary Tract Infections. *Urol Int*. 2015;95(2):167-176. doi:10.1159/000371894

424. Rudrabhatla P, Deepanjali S, Mandal J, Swaminathan RP, Kadhiravan T. Stopping the effective non-fluoroquinolone antibiotics at day 7 vs continuing until day 14 in adults with acute pyelonephritis requiring hospitalization: A randomized non-inferiority trial. *PLoS One*. 2018;13(5):e0197302. doi:10.1371/journal.pone.0197302

425. Lojanapiwat ◌̣b, Nimitvilai S, Bamroongya M, et al. Oral sitafloxacin vs intravenous ceftriaxone followed by oral cefdinir for acute pyelonephritis and complicated urinary tract infection: a randomized controlled trial. *IDR*. 2019;Volume 12:173-181. doi:10.2147/IDR.S178183

426. Moustafa F, Nguyen G, Mathevon T, et al. Evaluation of the efficacy and tolerance of a short 7 day third-generation cephalosporin treatment in the management of acute pyelonephritis in young women in the emergency department. *Journal of Antimicrobial Chemotherapy*. 2016;71(6):1660-1664. doi:10.1093/jac/dkw021

427. Vogler S, Pavich E. Pyelonephritis treatment in the community emergency department: Cephalosporins vs. first-line agents. *Am J Emerg Med*. 2018;36(11):2054-2057. doi:10.1016/j.ajem.2018.08.016

428. Lin K, Zahlanie Y, Ortwine JK, Wei W, Mang NS, Prokesch BC. A retrospective review of oral cephalosporins versus fluoroquinolones for the treatment of pyelonephritis. *PLoS One*. 2022;17(9):e0274194. doi:10.1371/journal.pone.0274194

429. Elbaz M, Zadka H, Weiss-Meilik A, Ben-Ami R. Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis. *J Antimicrob Chemother*. 2020;75(8):2307-2313. doi:10.1093/jac/dkaa148

430. Zohar I, Schwartz O, Yossepowitch O, David SSB, Maor Y. Aminoglycoside versus carbapenem or piperacillin/tazobactam treatment for bloodstream infections of urinary source caused by Gram-negative ESBL-producing Enterobacteriaceae. *J Antimicrob Chemother*. 2020;75(2):458-465. doi:10.1093/jac/dkz457

431. Wie SH, Kim HW, Chang UI. Effects of gentamicin monotherapy for the initial treatment of community-onset complicated non-obstructive acute pyelonephritis due to Enterobacteriaceae in elderly and non-elderly women. *Clin Microbiol Infect*. 2014;20(11):1211-1218. doi:10.1111/1469-0691.12711

432. Wald-Dickler N, Lee TC, Tangpraphaphorn S, et al. Fosfomycin vs Ertapenem for Outpatient Treatment of Complicated Urinary Tract Infections: A Multicenter, Retrospective Cohort Study. *Open Forum Infect Dis*. 2022;9(1):ofab620. doi:10.1093/ofid/ofab620

433. Sojo-Dorado J, López-Hernández I, Rosso-Fernandez C, et al. Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant Escherichia coli Bacteremic Urinary Tract Infections. *JAMA Netw Open*. 2022;5(1):e2137277. doi:10.1001/jamanetworkopen.2021.37277

434. Ten Doesschate T, Kuiper S, van Nieuwkoop C, et al. Fosfomycin Vs Ciprofloxacin as Oral Step-Down Treatment for Escherichia coli Febrile Urinary Tract Infections in Women: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. *Clin Infect Dis*. 2022;75(2):221-229. doi:10.1093/cid/ciab934

435. Seo J won, Young Kim D, Yoon Y, et al. 86. Effect of Oral Fosfomycin Compared to the Intravenous Beta Lactam/Beta-Lactamase Inhibitor or Carbapenem in Step-down Treatment of Patients with Complicated Urinary Tract Infection due to Extended-Spectrum Beta-Lactamase (ESBL) Producing Enterobacteriaceae: A Multicenter, Open-label, Randomized Controlled, Non-inferiority Trial. *Open Forum Infect Dis*. 2023;10(Suppl 2):ofad500.002. doi:10.1093/ofid/ofad500.002

436. van Nieuwkoop C, van der Starre WE, Stalenhoef JE, et al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. *BMC Med*. 2017;15(1):70. doi:10.1186/s12916-017-0835-3

437. Edlund C, Ternhag A, Skoog Ståhlgren G, et al. The clinical and microbiological efficacy of temocillin versus cefotaxime in adults with febrile urinary tract infection, and its effects on the intestinal microbiota: a randomised multicentre clinical trial in Sweden. *Lancet Infect Dis*. 2022;22(3):390-400. doi:10.1016/S1473-3099(21)00407-2

438. Clarke K, Hall CL, Wiley Z, et al. Catheter-Associated Urinary Tract Infections in Adults: Diagnosis, Treatment, and Prevention. *J Hosp Med*. 2020;15(9):552-556. doi:10.12788/jhm.3292

439. Mohler JL, Cowen DL, Flanigan RC. Suppression and Treatment of Urinary Tract Infection in Patients with an Intermittently Catheterized Neurogenic Bladder. *Journal of Urology*. 1987;138(2):336-340. doi:10.1016/S0022-5347(17)43138-7

440. Turjeman A, von Dach E, Molina J, et al. Duration of antibiotic treatment for Gram-negative bacteremia - Systematic review and individual participant data (IPD) meta-analysis. *EClinicalMedicine*. 2023;55:101750. doi:10.1016/j.eclinm.2022.101750

441. Daneman N, Rishu AH, Pinto RL, et al. Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomised clinical trial: study protocol. *BMJ Open*. 2020;10(5):e038300. doi:10.1136/bmjopen-2020-038300

442. McDonald EG, Prosty C, Hanula R, et al. Observational versus randomized controlled trials to inform antibiotic treatment durations: a narrative review. *Clin Microbiol Infect*. 2023;29(2):165-170. doi:10.1016/j.cmi.2022.09.002

443. Sutton JD, Stevens VW, Chang NCN, Khader K, Timbrook TT, Spivak ES. Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source. *JAMA Netw Open*. 2020;3(10):e2020166. doi:10.1001/jamanetworkopen.2020.20166

444. Saad S, Mina N, Lee C, Afra K. Oral beta-lactam step down in bacteremic E. coli urinary tract infections. *BMC Infect Dis*. 2020;20(1):785. doi:10.1186/s12879-020-05498-2

445. Mponponsuo K, Brown KA, Fridman DJ, et al. Highly versus less bioavailable oral antibiotics in the treatment of gram-negative bloodstream infections: a propensity-matched cohort analysis. *Clin Microbiol Infect*. 2023;29(4):490-497. doi:10.1016/j.cmi.2022.10.004

446. Mack T, Hiles JJ, Wrin J, Desai A. Use of Fluoroquinolones or Sulfamethoxazole-Trimethoprim Compared to B-Lactams for Oral Step-Down Therapy in Hospitalized Patients With Uncomplicated Enterobacterales Bacteremia. *Ann Pharmacother*. 2023;57(3):251-258. doi:10.1177/10600280221106789

447. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect Dis Clin North Am*. 2009;23(4):791-815, vii. doi:10.1016/j.idc.2009.06.008

448. Crandon JL, Nicolau DP. Pharmacodynamic approaches to optimizing beta-lactam therapy. *Crit Care Clin*. 2011;27(1):77-93. doi:10.1016/j.ccc.2010.11.004

449. Mogle BT, Beccari MV, Steele JM, Fazili T, Kufel WD. Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections. *Expert Opin Pharmacother*. 2019;20(8):903-907. doi:10.1080/14656566.2019.1594774

450. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis*. 2007;44(1):79-86. doi:10.1086/510079

451. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26(1):1-10; quiz 11-12. doi:10.1086/516284

452. Lodise TP, Lomaestro BM, Drusano GL, Society of Infectious Diseases Pharmacists. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26(9):1320-1332. doi:10.1592/phco.26.9.1320

453. Schatz BS, Karavokiros KT, Taeubel MA, Itokazu GS. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, cefixime, and ceftibuten. *Ann Pharmacother*. 1996;30(3):258-268. doi:10.1177/106002809603000310

454. Heil EL, Bork JT, Abbo LM, et al. Optimizing the Management of Uncomplicated Gram-Negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process. *Open Forum Infect Dis*. 2021;8(10):ofab434. doi:10.1093/ofid/ofab434

455. Al Lawati H, Blair BM, Larnard J. Urinary Tract Infections: Core Curriculum 2024. *Am J Kidney Dis*. 2024;83(1):90-100. doi:10.1053/j.ajkd.2023.08.009

456. Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):1611-1615. doi:10.1093/cid/ciz021

457. Liu F, MacDonald B, Jain R, et al. Prevalence and treatment of asymptomatic bacteriuria at academic and critical-access hospitals-Opportunities for stewardship efforts. *Infect Control Hosp Epidemiol*. 2023;44(6):979-981. doi:10.1017/ice.2022.143

458. Petty LA, Vaughn VM, Flanders SA, et al. Risk Factors and Outcomes Associated With Treatment of Asymptomatic Bacteriuria in Hospitalized Patients. *JAMA Intern Med*. 2019;179(11):1519-1527. doi:10.1001/jamainternmed.2019.2871

459. Petty LA, Vaughn VM, Flanders SA, et al. Assessment of Testing and Treatment of Asymptomatic Bacteriuria Initiated in the Emergency Department. *Open Forum Infect Dis*. 2020;7(12):ofaa537. doi:10.1093/ofid/ofaa537

460. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2019;2019(11). doi:10.1002/14651858.CD000490.pub4

461. Grabe M, Forsgren A, Hellsten S. The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*. 1984;18(1):37-42. doi:10.3109/00365598409182161

462. Grabe M, Forsgren A, Björk T, Hellsten S. Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. *Eur J Clin Microbiol*. 1987;6(1):11-17. doi:10.1007/BF02097183

463. Sayin Kutlu S, Aybek Z, Tekin K, et al. Is short course of antimicrobial therapy for asymptomatic bacteriuria before urologic surgical procedures sufficient? *J Infect Dev Ctries*. 2012;6(2):143-147. doi:10.3855/jidc.1781

464. Lightner DJ, Wymer K, Sanchez J, Kavoussi L. Best Practice Statement on Urologic Procedures and Antimicrobial Prophylaxis. *J Urol*. 2020;203(2):351-356. doi:10.1097/JU.0000000000000509

465. Shaikh N, Osio VA, Wessel CB, Jeong JH. Prevalence of Asymptomatic Bacteriuria in Children: A Meta-Analysis. *J Pediatr*. 2020;217:110-117.e4. doi:10.1016/j.jpeds.2019.10.019

466. Köves B, Cai T, Veeratterapillay R, et al. Benefits and Harms of Treatment of Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. *Eur Urol*. 2017;72(6):865-868. doi:10.1016/j.eururo.2017.07.014

467. Rao Z, Wang Z, Tang M, Shen L, Zhang K. Treatment of Asymptomatic Bacteriuria after Kidney Transplantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicina (Kaunas)*. 2023;59(9):1600. doi:10.3390/medicina59091600

468. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Screening for Asymptomatic Bacteriuria in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2019;322(12):1188-1194. doi:10.1001/jama.2019.13069

469. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2019;2019(11):CD000490. doi:10.1002/14651858.CD000490.pub4

470. Kazemier BM, Koningstein FN, Schneeberger C, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis*. 2015;15(11):1324-1333. doi:10.1016/S1473-3099(15)00070-5

471. Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev*. 2015;2015(11):CD000491. doi:10.1002/14651858.CD000491.pub3

472. Lumbiganon P, Villar J, Laopaiboon M, et al. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. *Obstet Gynecol*. 2009;113(2 Pt 1):339-345. doi:10.1097/AOG.0b013e318195c2a2

473. Bonkat G, Bartoletti R, Bruyère F, et al. EAU Guidelines on Urological Infections. Published online 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-infections-2023.pdf

474. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A Review of Antibiotic Use in Pregnancy. *Pharmacotherapy*. 2015;35(11):1052-1062. doi:10.1002/phar.1649

475. Corrales M, Corrales-Acosta E, Corrales-Riveros JG. Which Antibiotic for Urinary Tract Infections in Pregnancy? A Literature Review of International Guidelines. *J Clin Med*. 2022;11(23):7226. doi:10.3390/jcm11237226

476. Chong JT, Klausner AP, Petrossian A, et al. Pre-procedural antibiotics for endoscopic urological procedures: Initial experience in individuals with spinal cord injury and asymptomatic bacteriuria. *J Spinal Cord Med*. 2015;38(2):187-192. doi:10.1179/2045772313Y.0000000185

477. Hara N, Kitamura Y, Saito T, Komatsubara S, Nishiyama T, Takahashi K. Perioperative antibiotics in radical cystectomy with ileal conduit urinary diversion: efficacy and risk of antimicrobial prophylaxis on the operation day alone. *Int J Urol*. 2008;15(6):511-515. doi:10.1111/j.1442-2042.2008.02050.x

478. Takeyama K, Takahashi S, Maeda T, et al. Comparison of 1-day, 2-day, and 3-day administration of antimicrobial prophylaxis in radical prostatectomy. *J Infect Chemother*. 2007;13(5):320-323. doi:10.1007/s10156-007-0540-9

479. Agbugui JO, Obarisiagbon EO, Osaigbovo EO, Osime CO, Akumabor PN. Antibiotic prophylaxis for transrectal prostate biopsy: a comparison of one-day and five-day regimen. *Niger Postgrad Med J*. 2014;21(3):213-217.

480. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int*. 2000;85(6):682-685. doi:10.1046/j.1464-410x.2000.00576.x

481. Sakura M, Kawakami S, Yoshida S, Masuda H, Kobayashi T, Kihara K. Prospective comparative study of single dose versus 3-day administration of antimicrobial prophylaxis in minimum incision endoscopic radical prostatectomy. *Int J Urol*. 2008;15(4):328-331. doi:10.1111/j.1442-2042.2008.02001.x

482. Hall JC, Christiansen KJ, England P, et al. Antibiotic prophylaxis for patients undergoing transurethral resection of the prostate. *Urology*. 1996;47(6):852-856. doi:10.1016/S0090-4295(96)00066-0

483. Terai A, Ichioka K, Kohei N, Ueda N, Utsunomiya N, Inoue K. Antibiotic prophylaxis in radical prostatectomy: 1-day versus 4-day treatments. *Int J Urol*. 2006;13(12):1488-1493. doi:10.1111/j.1442-2042.2006.01597.x

484. Aus G, Ahlgren G, Bergdahl S, Hugosson J. Infection after transrectal core biopsies of the prostate--risk factors and antibiotic prophylaxis. *Br J Urol*. 1996;77(6):851-855. doi:10.1046/j.1464-410x.1996.01014.x

485. Yang L, Hu J, Wei H, Wang L, Zhong H. [Clinical significance of antibiotic prophylaxis for transrectal prostate biopsy]. *Zhonghua Wai Ke Za Zhi*. 2001;39(12):940-942.

486. Herranz Amo F, Rodríguez Fernández E, Díez Cordero JM, et al. [Morbidity of and tolerance to ultrasonography-guided transrectal biopsy of the prostate]. *Actas Urol Esp*. 1996;20(10):858-866.

487. Linden-Castro E, Pelayo-Nieto M, Alias-Melgar A, Carreño-de la Rosa F. Single Dose of Levofloxacin versus Three Dosages for Prophylaxis in Prostate Biopsy. *Int Sch Res Notices*. 2014;2014:875670. doi:10.1155/2014/875670

488. Jayanth ST, Chandrasingh J, Sahni RD, et al. Efficacy of 1 versus 3 days of intravenous amikacin as a prophylaxis for patients undergoing transurethral resection of the prostate: A prospective randomized trial. *Indian J Urol*. 2021;37(2):133-139. doi:10.4103/iju.IJU_494_20

489. Su R, Wang KY, Zhang D, Yan ZJ, Jiang JH, Ma Q. Comparison of levofloxacin-based prophylaxis regimens for transrectal prostate biopsy: a prospective randomized single-center study. *Eur J Clin Microbiol Infect Dis*. 2019;38(5):967-971. doi:10.1007/s10096-019-03541-y

490. Schaeffer AJ, Montorsi F, Scattoni V, et al. Comparison of a 3-day with a 1-day regimen of an extended-release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. *BJU Int*. 2007;100(1):51-57. doi:10.1111/j.1464-410X.2007.06848.x

491. Peters HJ, Breitling P. [Antibiotic prophylaxis in transrectal prostate biopsy. Short-term vs. long-term therapy]. *Urologe A*. 2003;42(1):91-94.

492. Briffaux R, Coloby P, Bruyere F, et al. One preoperative dose randomized against 3-day antibiotic prophylaxis for transrectal ultrasonography-guided prostate biopsy. *BJU Int*. 2009;103(8):1069-1073; discussion 1073. doi:10.1111/j.1464-410X.2008.08128.x

493. Mari M. [Single dose versus 5-day course of oral prulifloxacin in antimicrobial prophylaxis for transrectal prostate biopsy]. *Minerva Urol Nefrol*. 2007;59(1):1-10.

494. Cam K, Kayikci A, Akman Y, Erol A. Prospective assessment of the efficacy of single dose versus traditional 3-day antimicrobial prophylaxis in 12-core transrectal prostate biopsy. *Int J Urol*. 2008;15(11):997-1001. doi:10.1111/j.1442-2042.2008.02147.x

495. Sabbagh R, McCormack M, Péloquin F, et al. A prospective randomized trial of 1-day versus 3-day antibiotic prophylaxis for transrectal ultrasound guided prostate biopsy. *Can J Urol*. 2004;11(2):2216-2219.

496. Giannella M, Bussini L, Pascale R, et al. Prognostic Utility of the New Definition of Difficult-to-Treat Resistance Among Patients With Gram-Negative Bloodstream Infections. *Open Forum Infect Dis*. 2019;6(12):ofz505. doi:10.1093/ofid/ofz505

497. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. *Clin Infect Dis*. 2018;67(12):1803-1814. doi:10.1093/cid/ciy378

498. El Zowalaty ME, Al Thani AA, Webster TJ, et al. Pseudomonas aeruginosa: arsenal of resistance mechanisms, decades of changing resistance profiles, and future antimicrobial therapies. *Future Microbiol*. 2015;10(10):1683-1706. doi:10.2217/fmb.15.48

499. Qin S, Xiao W, Zhou C, et al. Pseudomonas aeruginosa: pathogenesis, virulence factors, antibiotic resistance, interaction with host, technology advances and emerging therapeutics. *Sig Transduct Target Ther*. 2022;7(1):1-27. doi:10.1038/s41392-022-01056-1

500. HAI Pathogens and Antimicrobial Resistance Report, 2018-2021 | NHSN | CDC. July 28, 2023. Accessed June 17, 2024. https://www.cdc.gov/nhsn/hai-report/data-tables-adult/table-5.html

501. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269-284. doi:10.1038/nrmicro3432

502. Walkty A, Adam H, Baxter M, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in canadian hospitals as part of the CANWARD study, 2011-2012. *Antimicrob Agents Chemother*. 2014;58(5):2554-2563. doi:10.1128/AAC.02744-13

503. M100Ed34 | Performance Standards for Antimicrobial Susceptibility Testing, 34th Edition. Clinical & Laboratory Standards Institute. Accessed March 19, 2024. https://clsi.org/standards/products/microbiology/documents/m100/

504. eucast: Clinical breakpoints and dosing of antibiotics. Accessed June 17, 2024. https://www.eucast.org/clinical_breakpoints

505. Breakpoints. USCAST. Accessed June 17, 2024. https://www.uscast.org/breakpoints.html

506. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis*. 2016;16(6):661-673. doi:10.1016/S1473-3099(16)30004-4

507. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. *Clin Infect Dis*. 2020;70(9):1799-1808. doi:10.1093/cid/ciz530

508. Sims M, Mariyanovski V, McLeroth P, et al. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. *J Antimicrob Chemother*. 2017;72(9):2616-2626. doi:10.1093/jac/dkx139

509. Timsit JF, Mootien J, Akrich B, et al. Ceftolozane/Tazobactam for the Treatment of Complicated Infections in Hospital Settings—A French Real-world Study. *Open Forum Infectious Diseases*. 2024;11(2):ofae037. doi:10.1093/ofid/ofae037

510. Van Anglen LJ, Schroeder CP, Couch KA. A Real-world Multicenter Outpatient Experience of Ceftolozane/Tazobactam. *Open Forum Infectious Diseases*. 2023;10(5):ofad173. doi:10.1093/ofid/ofad173

511. Haidar G, Philips NJ, Shields RK, et al. Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant Pseudomonas aeruginosa Infections: Clinical Effectiveness and Evolution of Resistance. *Clin Infect Dis*. 2017;65(1):110-120. doi:10.1093/cid/cix182

512. Gallagher JC, Satlin MJ, Elabor A, et al. Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant Pseudomonas aeruginosa Infections: A Multicenter Study. *Open Forum Infect Dis*. 2018;5(11):ofy280. doi:10.1093/ofid/ofy280

513. Puzniak L, Dillon R, Palmer T, Collings H, Enstone A. Real-world use of ceftolozane/tazobactam: a systematic literature review. *Antimicrobial Resistance & Infection Control*. 2021;10(1):68. doi:10.1186/s13756-021-00933-8

514. Ito R, Mustapha MM, Tomich AD, et al. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. *mBio*. 2017;8(4):e00749-17. doi:10.1128/mBio.00749-17

515. Zheng D, Bergen PJ, Landersdorfer CB, Hirsch EB. Differences in Fosfomycin Resistance Mechanisms between Pseudomonas aeruginosa and Enterobacterales. *Antimicrob Agents Chemother*. 2022;66(2):e0144621. doi:10.1128/AAC.01446-21

516. Abbott IJ, van Gorp E, Wijma RA, et al. Efficacy of single and multiple oral doses of fosfomycin against Pseudomonas aeruginosa urinary tract infections in a dynamic in vitro bladder infection model. *J Antimicrob Chemother*. 2020;75(7):1879-1888. doi:10.1093/jac/dkaa127

517. Papp-Wallace KM, Zeiser ET, Becka SA, et al. Ceftazidime-Avibactam in Combination With Fosfomycin: A Novel Therapeutic Strategy Against Multidrug-Resistant Pseudomonas aeruginosa. *J Infect Dis*. 2019;220(4):666-676. doi:10.1093/infdis/jiz149

518. Avery LM, Sutherland CA, Nicolau DP. Prevalence of in vitro synergistic antibiotic interaction between fosfomycin and nonsusceptible antimicrobials in carbapenem-resistant Pseudomonas aeruginosa. *J Med Microbiol*. 2019;68(6):893-897. doi:10.1099/jmm.0.000984

519. Okazaki M, Suzuki K, Asano N, et al. Effectiveness of fosfomycin combined with other antimicrobial agents against multidrug-resistant Pseudomonas aeruginosa isolates using the efficacy time index assay. *J Infect Chemother*. 2002;8(1):37-42. doi:10.1007/s101560200004

520. Samonis G, Maraki S, Karageorgopoulos DE, Vouloumanou EK, Falagas ME. Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa clinical isolates. *Eur J Clin Microbiol Infect Dis*. 2012;31(5):695-701. doi:10.1007/s10096-011-1360-5

521. Aslan AT, Akova M. The Role of Colistin in the Era of New β-Lactam/β-Lactamase Inhibitor Combinations. *Antibiotics*. 2022;11(2):277. doi:10.3390/antibiotics11020277

522. Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis*. 2006;6(9):589-601. doi:10.1016/S1473-3099(06)70580-1

523. Sorlí L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant Pseudomonas aeruginosa: Dose is critical. *J Infect*. 2019;79(3):253-261. doi:10.1016/j.jinf.2019.06.011

524. López Montesinos I, Gómez-Zorrilla S, Palacios-Baena ZR, et al. Aminoglycoside or Polymyxin Monotherapy for Treating Complicated Urinary Tract Infections Caused by Extensively Drug-Resistant Pseudomonas aeruginosa: A Propensity Score-Adjusted and Matched Cohort Study. *Infect Dis Ther*. 2022;11(1):335-350. doi:10.1007/s40121-021-00570-z

525. Crusio R, Rao S, Changawala N, et al. Epidemiology and outcome of infections with carbapenem-resistant Gram-negative bacteria treated with polymyxin B-based combination therapy. *Scand J Infect Dis*. 2014;46(1):1-8. doi:10.3109/00365548.2013.844350

526. Dubrovskaya Y, Chen TY, Scipione MR, et al. Risk factors for treatment failure of polymyxin B monotherapy for carbapenem-resistant Klebsiella pneumoniae infections. *Antimicrob Agents Chemother*. 2013;57(11):5394-5397. doi:10.1128/AAC.00510-13

527. Pastewski AA, Caruso P, Parris AR, et al. Parenteral polymyxin B use in patients with multidrug-resistant gram-negative bacteremia and urinary tract infections: a retrospective case series. *Ann Pharmacother*. 2008;42(9):1177-1187. doi:10.1345/aph.1K346

528. Falagas ME, Kyriakidou M, Voulgaris GL, Vokos F, Politi S, Kechagias KS. Clinical use of intravenous polymyxin B for the treatment of patients with multidrug-resistant Gram-negative bacterial infections: An evaluation of the current evidence. *J Glob Antimicrob Resist*. 2021;24:342-359. doi:10.1016/j.jgar.2020.12.026

529. Umar Z, Ashfaq S, Parikh A, et al. Stenotrophomonas Maltophilia and Urinary Tract Infections: A Systematic Review. *Cureus*. 2022;14(6):e26184. doi:10.7759/cureus.26184

530. Seifert H. Acinetobacter species as a cause of catheter-related infections. *Zentralbl Bakteriol*. 1995;283(2):161-168. doi:10.1016/s0934-8840(11)80197-0

531. Jiménez-Guerra G, Heras-Cañas V, Gutiérrez-Soto M, et al. Urinary tract infection by Acinetobacter baumannii and Pseudomonas aeruginosa: evolution of antimicrobial resistance and therapeutic alternatives. *J Med Microbiol*. 2018;67(6):790-797. doi:10.1099/jmm.0.000742

532. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii–calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *The Lancet Infectious Diseases*. Published online May 2023:S1473309923001846. doi:10.1016/S1473-3099(23)00184-6

533. Vardakas KZ, Mavroudis AD, Georgiou M, Falagas ME. Intravenous colistin combination antimicrobial treatment vs. monotherapy: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2018;51(4):535-547. doi:10.1016/j.ijantimicag.2017.12.020

534. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. *Antimicrob Agents Chemother*. 2014;58(9):5598-5601. doi:10.1128/AAC.02435-13

535. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. *Clin Infect Dis*. 2013;57(3):349-358. doi:10.1093/cid/cit253

536. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Epidemiol Infect*. 2013;141(6):1214-1222. doi:10.1017/S095026881200194X

537. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant Acinetobacter baumannii: A randomised controlled trial. *J Glob Antimicrob Resist*. 2019;17:66-71. doi:10.1016/j.jgar.2018.11.016

538. Shah MD, Coe KE, El Boghdadly Z, et al. Efficacy of combination therapy versus monotherapy in the treatment of Stenotrophomonas maltophilia pneumonia. *J Antimicrob Chemother*. 2019;74(7):2055-2059. doi:10.1093/jac/dkz116

539. Araoka H, Baba M, Okada C, Abe M, Kimura M, Yoneyama A. Evaluation of trimethoprim-sulfamethoxazole based combination therapy against Stenotrophomonas maltophilia: in vitro effects and clinical efficacy in cancer patients. *Int J Infect Dis*. 2017;58:18-21. doi:10.1016/j.ijid.2017.02.020

540. Muder RR, Harris AP, Muller S, et al. Bacteremia due to Stenotrophomonas (Xanthomonas) maltophilia: a prospective, multicenter study of 91 episodes. *Clin Infect Dis*. 1996;22(3):508-512. doi:10.1093/clinids/22.3.508

541. Prawang A, Chanjamlong N, Rungwara W, et al. Combination Therapy versus Monotherapy in the Treatment of Stenotrophomonas maltophilia Infections: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)*. 2022;11(12):1788. doi:10.3390/antibiotics11121788

542. Fitzpatrick MA, Suda KJ, Poggensee L, et al. Epidemiology and clinical outcomes associated with extensively drug-resistant (XDR) Acinetobacter in US Veterans' Affairs (VA) medical centers. *Infect Control Hosp Epidemiol*. 2021;42(3):305-310. doi:10.1017/ice.2020.450

543. Vivo A, Fitzpatrick MA, Suda KJ, et al. Epidemiology and outcomes associated with carbapenem-resistant Acinetobacter baumannii and carbapenem-resistant Pseudomonas aeruginosa: a retrospective cohort study. *BMC Infect Dis*. 2022;22(1):491. doi:10.1186/s12879-022-07436-w

544. López-Cortés LE, Cisneros JM, Fernández-Cuenca F, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant Acinetobacter baumannii: analysis of a multicentre prospective cohort. *J Antimicrob Chemother*. 2014;69(11):3119-3126. doi:10.1093/jac/dku233

545. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial Susceptibility of Acinetobacter calcoaceticus-Acinetobacter baumannii Complex and Stenotrophomonas maltophilia Clinical Isolates: Results From the SENTRY Antimicrobial Surveillance Program (1997-2016). *Open Forum Infect Dis*. 2019;6(Suppl 1):S34-S46. doi:10.1093/ofid/ofy293

546. Jung SY, Lee SH, Lee SY, et al. Antimicrobials for the treatment of drug-resistant Acinetobacter baumannii pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. *Crit Care*. 2017;21(1):319. doi:10.1186/s13054-017-1916-6

547. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. *Journal of Antimicrobial Chemotherapy*. 2018;73(1):22-32. doi:10.1093/jac/dkx368

548. Liu J, Shu Y, Zhu F, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and

network meta-analysis. *J Glob Antimicrob Resist*. 2021;24:136-147. doi:10.1016/j.jgar.2020.08.021

549. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. *N Engl J Med*. 2019;380(8):729-740. doi:10.1056/NEJMoa1801467

550. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. In Vitro Activity of Minocycline against U.S. Isolates of Acinetobacter baumannii-Acinetobacter calcoaceticus Species Complex, Stenotrophomonas maltophilia, and Burkholderia cepacia Complex: Results from the SENTRY Antimicrobial Surveillance Program, 2014 to 2018. *Antimicrob Agents Chemother*. 2019;63(11):e01154-19. doi:10.1128/AAC.01154-19

551. Brust K, Evans A, Plemmons R. Tigecycline in treatment of multidrug-resistant Gram-negative bacillus urinary tract infections: a systematic review. *J Antimicrob Chemother*. 2014;69(10):2606-2610. doi:10.1093/jac/dku189

552. Liu YX, Le KJ, Shi HY, et al. Efficacy and safety of tigecycline for complicated urinary tract infection: a systematic review. *Transl Androl Urol*. 2021;10(1):292-299. doi:10.21037/tau-20-959

553. Morrissey I, Olesky M, Hawser S, et al. In Vitro Activity of Eravacycline against Gram-Negative Bacilli Isolated in Clinical Laboratories Worldwide from 2013 to 2017. *Antimicrob Agents Chemother*. 2020;64(3):e01699-19. doi:10.1128/AAC.01699-19

554. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe: Report from the SENTRY Antimicrobial Surveillance Program, 2016 to 2018. *Antimicrob Agents Chemother*. 2020;64(5):e02488-19. doi:10.1128/AAC.02488-19

555. Deolankar MS, Carr RA, Fliorent R, Roh S, Fraimow H, Carabetta VJ. Evaluating the Efficacy of Eravacycline and Omadacycline against Extensively Drug-Resistant Acinetobacter baumannii Patient Isolates. *Antibiotics (Basel)*. 2022;11(10):1298. doi:10.3390/antibiotics11101298

556. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, Against Gram-Negative Bacilli Isolated by Clinical Laboratories in North America and Europe in 2015-2016: SIDERO-WT-2015. *Int J Antimicrob Agents*. 2019;53(4):456-466. doi:10.1016/j.ijantimicag.2018.11.007

557. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2018;18(12):1319-1328. doi:10.1016/S1473-3099(18)30554-1

558. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2):226-240. doi:10.1016/S1473-3099(20)30796-9

559. Shortridge D, Streit JM, Mendes R, Castanheira M. In Vitro Activity of Cefiderocol against U.S. and European Gram-Negative Clinical Isolates Collected in 2020 as Part of the SENTRY Antimicrobial Surveillance Program. *Microbiol Spectr*. 2022;10(2):e0271221. doi:10.1128/spectrum.02712-21

560. XACDURO® (sulbactam for injection; durlobactam for injection). Accessed March 18, 2024. https://www.xacduro.com/

561. Sarzynski SH, Warner S, Sun J, et al. Trimethoprim-Sulfamethoxazole Versus Levofloxacin for Stenotrophomonas maltophilia Infections: A Retrospective Comparative Effectiveness Study of Electronic Health Records from 154 US Hospitals. *Open Forum Infect Dis*. 2022;9(2):ofab644. doi:10.1093/ofid/ofab644

562. Hand E, Davis H, Kim T, Duhon B. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of Stenotrophomonas maltophilia infections. *J Antimicrob Chemother*. 2016;71(4):1071-1075. doi:10.1093/jac/dkv456

563. McAteer J, Lee JH, Cosgrove SE, et al. Defining the Optimal Duration of Therapy for Hospitalized Patients With Complicated Urinary Tract Infections and Associated Bacteremia. *Clin Infect Dis*. 2023;76(9):1604-1612. doi:10.1093/cid/ciad009

564. Álvarez Otero J, Lamas Ferreiro JL, Sanjurjo Rivo A, et al. Treatment duration of complicated urinary tract infections by extended-spectrum beta-lactamases producing enterobacterales. *PLoS One*. 2020;15(10):e0237365. doi:10.1371/journal.pone.0237365

565. CRE Technical Information | CRE | HAI | CDC. February 22, 2021. Accessed March 17, 2024. https://www.cdc.gov/hai/organisms/cre/technical-info.html

566. Kazmierczak KM, Karlowsky JA, de Jonge BLM, Stone GG, Sahm DF. Epidemiology of Carbapenem Resistance Determinants Identified in Meropenem-Nonsusceptible Enterobacterales Collected as Part of a Global Surveillance Program, 2012 to 2017. *Antimicrobial Agents and Chemotherapy*. 2021;65(7):10.1128/aac.02000-20. doi:10.1128/aac.02000-20

567. Peirano G, Chen L, Nobrega D, et al. Genomic Epidemiology of Global Carbapenemase-Producing Escherichia coli, 2015-2017. *Emerg Infect Dis*. 2022;28(5):924-931. doi:10.3201/eid2805.212535

568. Boutzoukas AE, Komarow L, Chen L, et al. International Epidemiology of Carbapenemase-Producing Escherichia coli. *Clinical Infectious Diseases*. 2023;77(4):499-509. doi:10.1093/cid/ciad288

569. van Duin D, Arias CA, Komarow L, et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. *Lancet Infect Dis*. 2020;20(6):731-741. doi:10.1016/S1473-3099(19)30755-8

570. Hamzaoui Z, Ocampo-Sosa A, Fernandez Martinez M, et al. Role of association of OmpK35 and OmpK36 alteration and blaESBL and/or blaAmpC genes in conferring carbapenem

resistance among non-carbapenemase-producing Klebsiella pneumoniae. *Int J Antimicrob Agents*. 2018;52(6):898-905. doi:10.1016/j.ijantimicag.2018.03.020

571. Black CA, So W, Dallas SS, et al. Predominance of Non-carbapenemase Producing Carbapenem-Resistant Enterobacterales in South Texas. *Front Microbiol*. 2021;11:623574. doi:10.3389/fmicb.2020.623574

572. Singh N, Gandhi S, McArthur E, et al. Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. *CMAJ*. 2015;187(9):648-656. doi:10.1503/cmaj.150067

573. Geerts AFJ, Eppenga WL, Heerdink R, et al. Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. *Eur J Clin Pharmacol*. 2013;69(9):1701-1707. doi:10.1007/s00228-013-1520-x

574. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. *Ann Pharmacother*. 2013;47(1):106-111. doi:10.1345/aph.1R352

575. Welch E, Sheth S, Ashong CN, Pham C. Retrospective Review on the Safety and Efficacy of Nitrofurantoin for the Treatment of Cystitis in the Veteran Population With or Without Renal Insufficiency. *Open Forum Infect Dis*. 2021;8(9):ofab442. doi:10.1093/ofid/ofab442

576. Srinivas P, Wu J, Neuner EA, Pallotta A, Richter SS, Tsigrelis C. 2266. Management of Ertapenem-Resistant, Meropenem-Susceptible Enterobacteriaceae. *Open Forum Infect Dis*. 2019;6(Suppl 2):S775-S776. doi:10.1093/ofid/ofz360.1944

577. Yang FC, Yan JJ, Hung KH, Wu JJ. Characterization of Ertapenem-Resistant Enterobacter cloacae in a Taiwanese University Hospital. *Journal of Clinical Microbiology*. 2012;50(2):223-226. doi:10.1128/jcm.01263-11

578. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. *Clin Infect Dis*. 2016;63(6):754-762. doi:10.1093/cid/ciw378

579. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. *JAMA*. 2018;319(8):788-799. doi:10.1001/jama.2018.0438

580. Karakonstantis S, Rousaki M, Vassilopoulou L, Kritsotakis EI. Global prevalence of cefiderocol non-susceptibility in Enterobacterales, Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia: a systematic review and meta-analysis. *Clinical Microbiology and Infection*. 2024;30(2):178-188. doi:10.1016/j.cmi.2023.08.029

581. Karakonstantis S, Rousaki M, Kritsotakis EI. Cefiderocol: Systematic Review of Mechanisms of Resistance, Heteroresistance and In Vivo Emergence of Resistance. *Antibiotics (Basel)*. 2022;11(6):723. doi:10.3390/antibiotics11060723

582. Bassetti M, Di Pilato V, Giani T, et al. Treatment of severe infections due to metallo-β-lactamases-producing Gram-negative bacteria. *Future Microbiol*. Published online November 3, 2020:1489-1505. doi:10.2217/fmb-2020-0210

583. Mauri C, Maraolo AE, Di Bella S, Luzzaro F, Principe L. The Revival of Aztreonam in Combination with Avibactam against Metallo-β-Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases. *Antibiotics (Basel)*. 2021;10(8):1012. doi:10.3390/antibiotics10081012

584. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother*. 2010;54(3):969-976. doi:10.1128/AAC.01009-09

585. Honoré N, Nicolas MH, Cole ST. Inducible cephalosporinase production in clinical isolates of Enterobacter cloacae is controlled by a regulatory gene that has been deleted from Escherichia coli. *EMBO J*. 1986;5(13):3709-3714. doi:10.1002/j.1460-2075.1986.tb04704.x

586. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership Group. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. *Clin Infect Dis*. 2019;69(8):1446-1455. doi:10.1093/cid/ciz173

587. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med*. 1991;115(8):585-590. doi:10.7326/0003-4819-115-8-585

588. Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y. Risk factors for emergence of resistance to broad-spectrum cephalosporins among Enterobacter spp. *Antimicrob Agents Chemother*. 2001;45(9):2628-2630. doi:10.1128/AAC.45.9.2628-2630.2001

589. Hilty M, Sendi P, Seiffert SN, et al. Characterisation and clinical features of Enterobacter cloacae bloodstream infections occurring at a tertiary care university hospital in Switzerland: is cefepime adequate therapy? *Int J Antimicrob Agents*. 2013;41(3):236-249. doi:10.1016/j.ijantimicag.2012.10.022

590. Tamma PD, Girdwood SCT, Gopaul R, et al. The use of cefepime for treating AmpC β-lactamase-producing Enterobacteriaceae. *Clin Infect Dis*. 2013;57(6):781-788. doi:10.1093/cid/cit395

591. Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. *Antimicrob Agents Chemother*. 2008;52(3):995-1000. doi:10.1128/AAC.01083-07

592. Drozdinsky G, Neuberger A, Rakedzon S, et al. Treatment of Bacteremia Caused by Enterobacter spp.: Should the Potential for AmpC Induction Dictate Therapy? A Retrospective Study. *Microb Drug Resist*. 2021;27(3):410-414. doi:10.1089/mdr.2020.0234

593. Peters DM, Winter JB, Droege CA, Ernst NE, Liao S. Comparison of Ceftriaxone and Antipseudomonal β-Lactam Antibiotics Utilized for Potential AmpC β-Lactamase-Producing Organisms. *Hosp Pharm*. 2021;56(5):560-568. doi:10.1177/0018578720931463

594. da Cunha Ferreira T, Martins IS. Risk Factors of Death in Bloodstream Infections Caused by AmpC β-Lactamase-Producing Enterobacterales in Patients with Neoplasia. *Infect Drug Resist*. 2021;14:3083-3097. doi:10.2147/IDR.S312920

595. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. *Clin Infect Dis*. 1995;21(5):1107-1113. doi:10.1093/clinids/21.5.1107

596. Kohlmann R, Bähr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase. *J Antimicrob Chemother*. 2018;73(6):1530-1536. doi:10.1093/jac/dky084

597. Thomson KS, Sanders CC, Washington JA. Ceftazidime resistance in Hafnia alvei. *Antimicrob Agents Chemother*. 1993;37(6):1375-1376. doi:10.1128/AAC.37.6.1375

598. Girlich D, Naas T, Bellais S, Poirel L, Karim A, Nordmann P. Heterogeneity of AmpC Cephalosporinases of Hafnia alvei Clinical Isolates Expressing Inducible or Constitutive Ceftazidime Resistance Phenotypes. *Antimicrob Agents Chemother*. 2000;44(11):3220-3223.

599. Cornelis G, Abraham EP. Beta-lactamases from Yersinia enterocolitica. *J Gen Microbiol*. 1975;87(2):273-284. doi:10.1099/00221287-87-2-273

600. Liu C, Wang X, Chen Y, et al. Three Yersinia enterocolitica AmpD Homologs Participate in the Multi-Step Regulation of Chromosomal Cephalosporinase, AmpC. *Front Microbiol*. 2016;7:1282. doi:10.3389/fmicb.2016.01282

601. Negri MC, Baquero F. In vitro selective concentrations of cefepime and ceftazidime for AmpC beta-lactamase hyperproducer Enterobacter cloacae variants. *Clin Microbiol Infect*. 1999;5 Suppl 1:S25-S28. doi:10.1111/j.1469-0691.1999.tb00721.x

602. Tamma PD, Sharara SL, Pana ZD, et al. Molecular Epidemiology of Ceftriaxone-Nonsusceptible Enterobacterales Isolates in an Academic Medical Center in the United States. *Open Forum Infectious Diseases*. 2019;6(8):ofz353. doi:10.1093/ofid/ofz353

603. Hardy ME, Kenney RM, Tibbetts RJ, Shallal AB, Veve MP. Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales. *Antimicrobial Agents and Chemotherapy*. 2023;67(11):e00826-23. doi:10.1128/aac.00826-23

604. Derrick C, Bookstaver PB, Lu ZK, et al. Multicenter, Observational Cohort Study Evaluating Third-Generation Cephalosporin Therapy for Bloodstream Infections Secondary to Enterobacter, Serratia, and Citrobacter Species. *Antibiotics (Basel)*. 2020;9(5):254. doi:10.3390/antibiotics9050254

605. Szabó R, Böröcz K. Antimicrobial use in Hungarian long-term care facilities: high proportion of quinolone antibacterials. *Arch Gerontol Geriatr*. 2014;59(1):190-193. doi:10.1016/j.archger.2014.02.011

606. Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and

Ceftriaxone Resistance: A Randomized Clinical Trial. *JAMA*. 2018;320(10):984-994. doi:10.1001/jama.2018.12163

607. Philippon A, Arlet G, Labia R, Iorga BI. Class C β-Lactamases: Molecular Characteristics. *Clin Microbiol Rev*. 2022;35(3):e0015021. doi:10.1128/cmr.00150-21

608. Lu B, Wong M, Ha D, et al. Piperacillin/tazobactam versus cefepime or carbapenems for cefoxitin-non-susceptible Enterobacter cloacae, Klebsiella aerogenes, Citrobacter freundii, Serratia marcescens and Morganella morganii bacteraemia in immunocompromised patients. *Journal of Antimicrobial Chemotherapy*. 2023;78(4):1009-1014. doi:10.1093/jac/dkad037

609. Stewart AG, Paterson DL, Young B, et al. Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing Enterobacter spp, Citrobacter freundii, Morganella morganii, Providencia spp, or Serratia marcescens: A Pilot Multicenter Randomized Controlled Trial (MERINO-2). *Open Forum Infectious Diseases*. 2021;8(8):ofab387. doi:10.1093/ofid/ofab387

610. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC β-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2017;61(6):e00276-17. doi:10.1128/AAC.00276-17

611. Castanheira M, Kimbrough JH, DeVries S, Mendes RE, Sader HS. Trends of β-Lactamase Occurrence Among Escherichia coli and Klebsiella pneumoniae in United States Hospitals During a 5-Year Period and Activity of Antimicrobial Agents Against Isolates Stratified by β-Lactamase Type. *Open Forum Infectious Diseases*. 2023;10(2):ofad038. doi:10.1093/ofid/ofad038

612. Bradford PA. Extended-Spectrum β-Lactamases in the 21st Century: Characterization, Epidemiology, and Detection of This Important Resistance Threat. *Clin Microbiol Rev*. 2001;14(4):933-951. doi:10.1128/CMR.14.4.933-951.2001

613. Talan DA, Takhar SS, Krishnadasan A, Abrahamian FM, Mower WR, Moran GJ. Fluoroquinolone-Resistant and Extended-Spectrum β-Lactamase-Producing Escherichia coli Infections in Patients with Pyelonephritis, United States(1). *Emerg Infect Dis*. 2016;22(9):1594-1603. doi:10.3201/eid2209.160148

614. Araújo MRB, Sant'Anna L de O, Santos NNCD, Seabra LF, Santos LSD. Monitoring fluoroquinolone resistance among ESBL-positive and ESBL-negative Escherichia coli strains isolated from urinary tract infections: An alert for empirical treatment. *Rev Soc Bras Med Trop*. 2023;56:e0513. doi:10.1590/0037-8682-0513-2022

615. Paterson DL. "Collateral Damage" from Cephalosporin or Quinolone Antibiotic Therapy. *Clinical Infectious Diseases*. 2004;38(Supplement_4):S341-S345. doi:10.1086/382690

616. Paterson DL. Impact of antibiotic resistance in gram-negative bacilli on empirical and definitive antibiotic therapy. *Clin Infect Dis*. 2008;47 Suppl 1:S14-20. doi:10.1086/590062

617. Son SK, Lee NR, Ko JH, et al. Clinical effectiveness of carbapenems versus alternative antibiotics for treating ESBL-producing Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*. 2018;73(10):2631-2642. doi:10.1093/jac/dky168

618. Williams MC, Dominguez SR, Prinzi A, Lee K, Parker SK. Reliability of mecA in Predicting Phenotypic Susceptibilities of Coagulase-Negative Staphylococci and Staphylococcus aureus. *Open Forum Infectious Diseases*. 2020;7(12):ofaa553. doi:10.1093/ofid/ofaa553

619. Duplessis C, Crum-Cianflone NF. Ceftaroline: A New Cephalosporin with Activity against Methicillin-Resistant Staphylococcus aureus (MRSA). *Clin Med Rev Ther*. 2011;3:a2466. doi:10.4137/CMRT.S1637

620. Kisgen J, Whitney D. Ceftobiprole, a Broad-Spectrum Cephalosporin With Activity against Methicillin-Resistant Staphylococcus aureus (MRSA). *P T*. 2008;33(11):631-641.

621. Schuler F, Barth PJ, Niemann S, Schaumburg F. A Narrative Review on the Role of Staphylococcus aureus Bacteriuria in S. aureus Bacteremia. *Open Forum Infectious Diseases*. 2021;8(6):ofab158. doi:10.1093/ofid/ofab158

622. Muder RR, Brennen C, Rihs JD, et al. Isolation of Staphylococcus aureus from the urinary tract: association of isolation with symptomatic urinary tract infection and subsequent staphylococcal bacteremia. *Clin Infect Dis*. 2006;42(1):46-50. doi:10.1086/498518

623. Stokes W, Parkins MD, Parfitt ECT, Ruiz JC, Mugford G, Gregson DB. Incidence and Outcomes of Staphylococcus aureus Bacteriuria: A Population-based Study. *Clin Infect Dis*. 2019;69(6):963-969. doi:10.1093/cid/ciy1000

624. Mason CY, Sobti A, Goodman AL. Staphylococcus aureus bacteriuria: implications and management. *JAC Antimicrob Resist*. 2023;5(1):dlac123. doi:10.1093/jacamr/dlac123

625. Doern GV, Carroll KC, Diekema DJ, et al. Practical Guidance for Clinical Microbiology Laboratories: A Comprehensive Update on the Problem of Blood Culture Contamination and a Discussion of Methods for Addressing the Problem. *Clin Microbiol Rev*. 2019;33(1):e00009-19. doi:10.1128/CMR.00009-19

626. McDonald EG, Aggrey G, Tarik Aslan A, et al. Guidelines for Diagnosis and Management of Infective Endocarditis in Adults: A WikiGuidelines Group Consensus Statement. *JAMA Netw Open*. 2023;6(7):e2326366. doi:10.1001/jamanetworkopen.2023.26366

627. Miller WR, Munita JM, Arias CA. Mechanisms of antibiotic resistance in enterococci. *Expert Rev Anti Infect Ther*. 2014;12(10):1221-1236. doi:10.1586/14787210.2014.956092

628. Richey EM, Waters PW, Jovic M, Rakhman C. Treatment of Ampicillin-Resistant Enterococcus faecium Urinary Tract Infections. *Fed Pract*. 2015;32(6):20-23.

629. Cole KA, Kenney RM, Perri MB, et al. Outcomes of Aminopenicillin Therapy for Vancomycin-Resistant Enterococcal Urinary Tract Infections. *Antimicrob Agents Chemother*. 2015;59(12):7362-7366. doi:10.1128/AAC.01817-15

630. Shah KJ, Cherabuddi K, Shultz J, Borgert S, Ramphal R, Klinker KP. Ampicillin for the treatment of complicated urinary tract infections caused by vancomycin-resistant Enterococcus spp (VRE): a single-center university hospital experience. *Int J Antimicrob Agents*. 2018;51(1):57-61. doi:10.1016/j.ijantimicag.2017.06.008

631. de Oca JEM, Veve MP, Zervos MJ, Kenney RM. Aminopenicillins vs non-aminopenicillins for treatment of enterococcal lower urinary tract infections. *Int J Antimicrob Agents*. 2023;61(6):106800. doi:10.1016/j.ijantimicag.2023.106800

632. Heintz BH, Halilovic J, Christensen CL. Vancomycin-resistant enterococcal urinary tract infections. *Pharmacotherapy*. 2010;30(11):1136-1149. doi:10.1592/phco.30.11.1136

633. Heintz BH, Cho S, Fujioka A, Li J, Halilovic J. Evaluation of the treatment of vancomycin-resistant enterococcal urinary tract infections in a large academic medical center. *Ann Pharmacother*. 2013;47(2):159-169. doi:10.1345/aph.1R419

634. Wingler MJ, Patel NR, King ST, Wagner JL, Barber KE, Stover KR. Linezolid for the Treatment of Urinary Tract Infections Caused by Vancomycin-Resistant Enterococci. *Pharmacy (Basel)*. 2021;9(4):175. doi:10.3390/pharmacy9040175

635. Moehring RW, Yarrington ME, Warren BG, et al. Evaluation of an Opt-Out Protocol for Antibiotic De-Escalation in Patients With Suspected Sepsis: A Multicenter, Randomized, Controlled Trial. *Clin Infect Dis*. 2023;76(3):433-442. doi:10.1093/cid/ciac787

636. Leone M, Bechis C, Baumstarck K, et al. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med*. 2014;40(10):1399-1408. doi:10.1007/s00134-014-3411-8

637. Chopra V, O'Horo JC, Rogers MAM, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2013;34(9):908-918. doi:10.1086/671737

638. Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. *Am J Med*. 2012;125(8):733-741. doi:10.1016/j.amjmed.2012.04.010

639. Chopra V, Flanders SA, Saint S. The problem with peripherally inserted central catheters. *JAMA*. 2012;308(15):1527-1528. doi:10.1001/jama.2012.12704

640. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311-325. doi:10.1016/S0140-6736(13)60592-9

641. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Internal Medicine*. 2017;177(9):1308-1315. doi:10.1001/jamainternmed.2017.1938

642. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *American Journal of Health-System Pharmacy*. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036

643. Keller SC, Williams D, Gavgani M, et al. Rates of and Risk Factors for Adverse Drug Events in Outpatient Parenteral Antimicrobial Therapy. *Clin Infect Dis*. 2018;66(1):11-19. doi:10.1093/cid/cix733

644. Rieger KL, Bosso JA, MacVane SH, Temple Z, Wahlquist A, Bohm N. Intravenous-only or Intravenous Transitioned to Oral Antimicrobials for Enterobacteriaceae-Associated Bacteremic Urinary Tract Infection. *Pharmacotherapy*. 2017;37(11):1479-1483. doi:10.1002/phar.2024

645. Gamble KC, Rose DT, Sapozhnikov J. Intravenous to oral antibiotics versus intravenous antibiotics: a step-up or a step-down for extended spectrum β-lactamase (ESBL)-producing urinary tract infections without concomitant bacteraemia? *International Journal of Antimicrobial Agents*. 2022;59(3):106541. doi:10.1016/j.ijantimicag.2022.106541

646. Mouwen AMA, Dijkstra JA, Jong E, Buijtels PC a. M, Pasker-de Jong PCM, Nagtegaal JE. Early switching of antibiotic therapy from intravenous to oral using a combination of education, pocket-sized cards and switch advice: A practical intervention resulting in reduced length of hospital stay. *Int J Antimicrob Agents*. 2020;55(1):105769. doi:10.1016/j.ijantimicag.2019.07.020

647. Gandhi K, Wrzesinski M, Bunnell K, Gibble A. Oral antibiotic step-down therapy for nonstaphylococcal gram-positive bloodstream infections. *Diagn Microbiol Infect Dis*. 2023;107(4):116068. doi:10.1016/j.diagmicrobio.2023.116068

648. Olson J, Franz-O'Neal E, Cipriano FA, Ou Z, Presson AP, Thorell EA. Impact of Early Oral Antibiotic Therapy in Infants With Bacteremic Urinary Tract Infections. *Hosp Pediatr*. 2022;12(7):632-638. doi:10.1542/hpeds.2021-006479

649. McAlister MJ, Rose DT, Hudson FP, Padilla-Tolentino E, Jaso TC. Oral β-lactams vs fluoroquinolones and trimethoprim/sulfamethoxazole for step-down therapy for Escherichia coli, Proteus mirabilis, and Klebsiella pneumoniae bacteremia. *Am J Health Syst Pharm*. 2023;80(Suppl 1):S33-S41. doi:10.1093/ajhp/zxac202

650. Eron LJ, Passos S. Early discharge of infected patients through appropriate antibiotic use. *Arch Intern Med*. 2001;161(1):61-65. doi:10.1001/archinte.161.1.61

651. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. *J Allergy Clin Immunol*. 2022;150(6):1333-1393. doi:10.1016/j.jaci.2022.08.028

652. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393(10167):183-198. doi:10.1016/S0140-6736(18)32218-9

653. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The Cost of Penicillin Allergy Evaluation. *J Allergy Clin Immunol Pract*. 2018;6(3):1019-1027.e2. doi:10.1016/j.jaip.2017.08.006

654. Hayden DA, White BP, Neely S, Bennett KK. Impact of Fluoroquinolone Susceptibility Suppression on Discharge Prescribing for Acute Uncomplicated Cystitis. *Open Forum Infect Dis*. 2023;10(10):ofad459. doi:10.1093/ofid/ofad459

655. Langford BJ, Seah J, Chan A, Downing M, Johnstone J, Matukas LM. Antimicrobial Stewardship in the Microbiology Laboratory: Impact of Selective Susceptibility Reporting on Ciprofloxacin Utilization and Susceptibility of Gram-Negative Isolates to Ciprofloxacin in a Hospital Setting. *J Clin Microbiol*. 2016;54(9):2343-2347. doi:10.1128/JCM.00950-16

656. Alshareef H, Alfahad W, Albaadani A, Alyazid H, Talib RB. Impact of antibiotic de-escalation on hospitalized patients with urinary tract infections: A retrospective cohort single center study. *J Infect Public Health*. 2020;13(7):985-990. doi:10.1016/j.jiph.2020.03.004

657. Sadyrbaeva-Dolgova S, Aznarte-Padial P, Jimenez-Morales A, Expósito-Ruiz M, Calleja-Hernández MÁ, Hidalgo-Tenorio C. Pharmacist recommendations for carbapenem de-escalation in urinary tract infection within an antimicrobial stewardship program. *Journal of Infection and Public Health*. 2020;13(4):558-563. doi:10.1016/j.jiph.2019.09.014

658. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database Syst Rev*. 2007;2007(4):CD003237. doi:10.1002/14651858.CD003237.pub2

659. Paul M, Dickstein Y, Raz-Pasteur A. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. *Clinical Microbiology and Infection*. 2016;22(12):960-967. doi:10.1016/j.cmi.2016.05.023

660. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance. *Pharmacotherapy*. 2019;39(3):261-270. doi:10.1002/phar.2201

661. Sijbom M, Büchner FL, Saadah NH, Numans ME, De Boer MGJ. Trends in antibiotic selection pressure generated in primary care and their association with sentinel antimicrobial resistance patterns in Europe. *J Antimicrob Chemother*. 2023;78(5):1245-1252. doi:10.1093/jac/dkad082

662. Paharik AE, Schreiber HL, Spaulding CN, Dodson KW, Hultgren SJ. Narrowing the spectrum: the new frontier of precision antimicrobials. *Genome Med*. 2017;9(1):110. doi:10.1186/s13073-017-0504-3

663. Bergman M, Huikko S, Pihlajamäki M, et al. Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997-2001. *Clin Infect Dis*. 2004;38(9):1251-1256. doi:10.1086/383309

664. Levy SB, FitzGerald GB, Macone AB. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *N Engl J Med*. 1976;295(11):583-588. doi:10.1056/NEJM197609092951103

665. Silbergeld EK, Graham J, Price LB. Industrial food animal production, antimicrobial resistance, and human health. *Annu Rev Public Health*. 2008;29:151-169. doi:10.1146/annurev.publhealth.29.020907.090904

666. Hammerum AM, Heuer OE, Emborg HD, et al. Danish integrated antimicrobial resistance monitoring and research program. *Emerg Infect Dis*. 2007;13(11):1632-1639. doi:10.3201/eid1311.070421

667. Gupta A, Nelson JM, Barrett TJ, et al. Antimicrobial resistance among Campylobacter strains, United States, 1997-2001. *Emerg Infect Dis*. 2004;10(6):1102-1109. doi:10.3201/eid1006.030635

668. Butler CC, Dunstan F, Heginbothom M, et al. Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices. *Br J Gen Pract*. 2007;57(543):785-792.

669. Dagan R, Barkai G, Givon-Lavi N, et al. Seasonality of antibiotic-resistant streptococcus pneumoniae that causes acute otitis media: a clue for an antibiotic-restriction policy? *J Infect Dis*. 2008;197(8):1094-1102. doi:10.1086/528995

670. Terahara F, Nishiura H. Fluoroquinolone consumption and Escherichia coli resistance in Japan: an ecological study. *BMC Public Health*. 2019;19(1):426. doi:10.1186/s12889-019-6804-3

671. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microb Drug Resist*. 1997;3(2):117-123. doi:10.1089/mdr.1997.3.117

672. Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med*. 1997;337(7):441-446. doi:10.1056/NEJM199708143370701

673. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014;14:13. doi:10.1186/1471-2334-14-13

674. Engers DW, Tamma PD, Fiawoo S, et al. Transition to Oral Antibiotic Therapy for Hospitalized Adults With Gram-Negative Bloodstream Infections. *JAMA Netw Open*. 2024;7(1):e2349864. doi:10.1001/jamanetworkopen.2023.49864

675. Davar K, Clark D, Centor RM, et al. Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV. *Open Forum Infect Dis*. 2023;10(1):ofac706. doi:10.1093/ofid/ofac706

676. Li J, Fan YY, Xin MZ, et al. A randomised, controlled trial comparing the long-term effects of peripherally inserted central catheter placement in chemotherapy patients using B-mode ultrasound with modified Seldinger technique versus blind puncture. *Eur J Oncol Nurs*. 2014;18(1):94-103. doi:10.1016/j.ejon.2013.08.003

677. Leung TK, Lee CM, Tai CJ, Liang YL, Lin CC. A retrospective study on the long-term placement of peripherally inserted central catheters and the importance of nursing care and education. *Cancer Nurs*. 2011;34(1):E25-30. doi:10.1097/NCC.0b013e3181f1ad6f

678. Broermann LE, Al-Hasan MN, Withers S, et al. Intravenous versus Partial Oral Antibiotic Therapy in the Treatment of Uncomplicated Bloodstream Infection Due to Streptococcus Species. *Microorganisms*. 2023;11(9):2313. doi:10.3390/microorganisms11092313

679. Deshpande A, Klompas M, Guo N, et al. Intravenous to Oral Antibiotic Switch Therapy Among Patients Hospitalized With Community-Acquired Pneumonia. *Clin Infect Dis*. 2023;77(2):174-185. doi:10.1093/cid/ciad196

680. Lau BD, Pinto BL, Thiemann DR, Lehmann CU. Budget impact analysis of conversion from intravenous to oral medication when clinically eligible for oral intake. *Clin Ther*. 2011;33(11):1792-1796. doi:10.1016/j.clinthera.2011.09.030

681. Fischer MA, Solomon DH, Teich JM, Avorn J. Conversion from intravenous to oral medications: assessment of a computerized intervention for hospitalized patients. *Arch Intern Med*. 2003;163(21):2585-2589. doi:10.1001/archinte.163.21.2585

682. Suleyman G, Kenney R, Zervos MJ, Weinmann A. Safety and efficacy of outpatient parenteral antibiotic therapy in an academic infectious disease clinic. *J Clin Pharm Ther*. 2017;42(1):39-43. doi:10.1111/jcpt.12465

683. MacFadden DR, LaDelfa A, Leen J, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. *Clin Infect Dis*. 2016;63(7):904-910. doi:10.1093/cid/ciw462

684. Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: A worldwide report. *Front Public Health*. 2022;10:888205. doi:10.3389/fpubh.2022.888205

685. Goebel MC, Trautner BW, Grigoryan L. The Five Ds of Outpatient Antibiotic Stewardship for Urinary Tract Infections. *Clin Microbiol Rev*. 2021;34(4):e0000320. doi:10.1128/CMR.00003-20

686. Ormeño MA, Ormeño MJ, Quispe AM, et al. Recurrence of Urinary Tract Infections due to Escherichia coli and Its Association with Antimicrobial Resistance. *Microb Drug Resist*. 2022;28(2):185-190. doi:10.1089/mdr.2021.0052

687. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51-77. doi:10.1093/cid/ciw118

688. Sousa-Pinto B, Blumenthal KG, Macy E, et al. Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study. *Clin Infect Dis*. 2021;72(6):924-938. doi:10.1093/cid/ciaa194

689. Song YC, Nelson ZJ, Wankum MA, Gens KD. Effectiveness and Feasibility of Pharmacist-Driven Penicillin Allergy De-Labeling Pilot Program without Skin Testing or Oral Challenges. *Pharmacy (Basel)*. 2021;9(3):127. doi:10.3390/pharmacy9030127

690. Zhou L, Dhopeshwarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy*. 2016;71(9):1305-1313. doi:10.1111/all.12881

691. Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009;122(8):778.e1-7. doi:10.1016/j.amjmed.2009.01.034

692. Blumenthal KG, Kuper K, Schulz LT, et al. Association Between Penicillin Allergy Documentation and Antibiotic Use. *JAMA Intern Med*. 2020;180(8):1120-1122. doi:10.1001/jamainternmed.2020.2227

693. Castells M, Khan DA, Phillips EJ. Penicillin Allergy. *N Engl J Med*. 2019;381(24):2338-2351. doi:10.1056/NEJMra1807761

694. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med*. 2003;349(17):1628-1635. doi:10.1056/NEJMoa022963

695. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. doi:10.1086/323353

696. Bonfanti P, Pusterla L, Parazzini F, et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study. C.I.S.A.I. Group. *Biomed Pharmacother*. 2000;54(1):45-49. doi:10.1016/s0753-3322(00)88640-0

697. Krantz MS, Stone CA, Abreo A, Phillips EJ. Oral challenge with trimethoprim-sulfamethoxazole in patients with “sulfa” antibiotic allergy. *J Allergy Clin Immunol Pract*. 2020;8(2):757-760.e4. doi:10.1016/j.jaip.2019.07.003

698. Dorn JM, Alpern M, McNulty C, Volcheck GW. Sulfonamide Drug Allergy. *Curr Allergy Asthma Rep*. 2018;18(7):38. doi:10.1007/s11882-018-0791-9

699. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM. The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998-2011. *Open Forum Infect Dis*. 2017;4(1):ofw281. doi:10.1093/ofid/ofw281

700. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tamma PD. Is Piperacillin-Tazobactam Effective for the Treatment of Pyelonephritis Caused by Extended-Spectrum β-Lactamase-Producing Organisms? *Clin Infect Dis*. 2020;71(8):e331-e337. doi:10.1093/cid/ciz1205

701. Anderson DT, Albrecht B, Jones KA, et al. Efficacy of Noncarbapenem β-Lactams Compared to Carbapenems for Extended-Spectrum β-Lactamase-Producing Enterobacterales Urinary Tract Infections. *Open Forum Infect Dis*. 2022;9(3):ofac034. doi:10.1093/ofid/ofac034

702. Branton AC, Vu CH, Venugopalan V, et al. Re-evaluation of cefepime or piperacillin/tazobactam to decrease use of carbapenems in ESBL-producing Enterobacterales urinary tract infections (REDUCE-UTI). *JAC Antimicrob Resist*. 2023;5(2):dlad021. doi:10.1093/jacamr/dlad021

703. Gould M, Ginn AN, Marriott D, Norris R, Sandaradura I. Urinary piperacillin/tazobactam pharmacokinetics in vitro to determine the pharmacodynamic breakpoint for resistant Enterobacteriaceae. *Int J Antimicrob Agents*. 2019;54(2):240-244. doi:10.1016/j.ijantimicag.2019.05.013

704. Kim SJ, Parikh P, King AN, Marnach ML. Asymptomatic Bacteriuria in Pregnancy Complicated by Pyelonephritis Requiring Nephrectomy. *Case Rep Obstet Gynecol*. 2018;2018:8924823. doi:10.1155/2018/8924823

705. Yoon YK, Kim JH, Sohn JW, Yang KS, Kim MJ. Role of piperacillin/tazobactam as a carbapenem-sparing antibiotic for treatment of acute pyelonephritis due to extended-spectrum β-lactamase-producing Escherichia coli. *Int J Antimicrob Agents*. 2017;49(4):410-415. doi:10.1016/j.ijantimicag.2016.12.017

706. Bryson AL, Bhalodi A, Liesman RM, Mathers AJ. Cefazolin as a predictor of urinary cephalosporin activity in indicated Enterobacterales. *Journal of Clinical Microbiology*. 2024;0(0):e00788-21. doi:10.1128/jcm.00788-21

707. Nicolle LE. ASYMPTOMATIC BACTERIURIA IN THE ELDERLY. *Infectious Disease Clinics of North America*. 1997;11(3):647-662. doi:10.1016/S0891-5520(05)70378-0

708. Ariathianto Y. Asymptomatic bacteriuria - prevalence in the elderly population. *Aust Fam Physician*. 2011;40(10):805-809.

709. Lin YT, Chen LK, Lin MH, Hwang SJ. Asymptomatic bacteriuria among the institutionalized elderly. *J Chin Med Assoc*. 2006;69(5):213-217. doi:10.1016/S1726-4901(09)70221-7

710. Childs SJ, Egan RJ. Bacteriuria and urinary infections in the elderly. *Urol Clin North Am*. 1996;23(1):43-54. doi:10.1016/s0094-0143(05)70292-5

711. Boscia JA, Kobasa WD, Abrutyn E, Levison ME, Kaplan AM, Kaye D. Lack of association between bacteriuria and symptoms in the elderly. *Am J Med*. 1986;81(6):979-982. doi:10.1016/0002-9343(86)90391-8

712. Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D. Epidemiology of bacteriuria in an elderly ambulatory population. *The American Journal of Medicine*. 1986;80(2):208-214. doi:10.1016/0002-9343(86)90011-2

713. Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. *Aging health*. 2013;9(5). doi:10.2217/ahe.13.38

714. Buul LW van, Vreeken HL, Bradley SF, et al. The Development of a Decision Tool for the Empiric Treatment of Suspected Urinary Tract Infection in Frail Older Adults: A Delphi Consensus Procedure. *Journal of the American Medical Directors Association*. 2018;19(9):757-764. doi:10.1016/j.jamda.2018.05.001

715. Rowe TA, Jump RLP, Andersen BM, et al. Reliability of nonlocalizing signs and symptoms as indicators of the presence of infection in nursing-home residents. *Infect Control Hosp Epidemiol*. 2022;43(4):417-426. doi:10.1017/ice.2020.1282

716. Amenta EM, Jump RLP, Trautner BW. Bacteriuria in older adults triggers confusion in healthcare providers: A mindful pause to treat the worry. *ASHE*. 2023;3(1):e4. doi:10.1017/ash.2022.343

717. Assessment and Management of the Resident With a Suspected Urinary Tract Infection. Accessed October 28, 2023. https://www.ahrq.gov/antibiotic-use/long-term-care/best-practices/uti-assess.html

718. Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *BMJ*. 2005;331(7518):669. doi:10.1136/bmj.38602.586343.55

719. Lohfeld L, Loeb M, Brazil K. Evidence-Based Clinical Pathways To Manage Urinary Tract Infections in Long-Term Care Facilities: A Qualitative Case Study Describing Administrator and Nursing Staff Views. *Journal of the American Medical Directors Association*. 2007;8(7):477-484. doi:10.1016/j.jamda.2007.05.006

720. van Buul LW, Vreeken HL, Bradley SF, et al. The Development of a Decision Tool for the Empiric Treatment of Suspected Urinary Tract Infection in Frail Older Adults: A Delphi Consensus Procedure. *J Am Med Dir Assoc*. 2018;19(9):757-764. doi:10.1016/j.jamda.2018.05.001

721. Genao L, Buhr GT. Urinary Tract Infections in Older Adults Residing in Long-Term Care Facilities. *Ann Longterm Care*. 2012;20(4):33-38.

722. Juthani-Mehta M, Tinetti M, Perrelli E, Towle V, Quagliarello V. Role of Dipstick Testing in the Evaluation of Urinary Tract Infection in Nursing Home Residents. *Infect Control Hosp Epidemiol*. 2007;28(7):889-891. doi:10.1086/518752

723. Phillips CD, Adepoju O, Stone N, et al. Asymptomatic bacteriuria, antibiotic use, and suspected urinary tract infections in four nursing homes. *BMC Geriatrics*. 2012;12(1):73. doi:10.1186/1471-2318-12-73

724. Ostrow O, Prodanuk M, Foong Y, et al. Decreasing Misdiagnoses of Urinary Tract Infections in a Pediatric Emergency Department. *Pediatrics*. 2022;150(1):e2021055866. doi:10.1542/peds.2021-055866

725. Choi DM, Heo TH, Yim HE, Yoo KH. Evaluation of new American Academy of Pediatrics guideline for febrile urinary tract infection. *Korean J Pediatr*. 2015;58(9):341. doi:10.3345/kjp.2015.58.9.341

726. Brandström P, Lindén M. How Swedish guidelines on urinary tract infections in children compare to Canadian, American and European guidelines. *Acta Paediatr*. 2021;110(6):1759-1771. doi:10.1111/apa.15727

727. 't Hoen LA, Bogaert G, Radmayr C, et al. Update of the EAU/ESPU guidelines on urinary tract infections in children. *J Pediatr Urol*. 2021;17(2):200-207. doi:10.1016/j.jpurol.2021.01.037

728. Spencer JD, Schwaderer A, McHugh K, Hains DS. Pediatric urinary tract infections: an analysis of hospitalizations, charges, and costs in the USA. *Pediatr Nephrol*. 2010;25(12):2469-2475. doi:10.1007/s00467-010-1625-8

729. Forster CS, Almaazi A, Hamdy R, Harik N. Predictors of Empiric Antibiotic Use in the Emergency Department in Children Without Urinary Tract Infections. *Pediatr Emer Care*. 2022;38(5):e1251-e1256. doi:10.1097/PEC.0000000000002586

730. Saha D, Patel J, Buckingham D, Thornton D, Barber T, Watson JR. Urine Culture Follow-up and Antimicrobial Stewardship in a Pediatric Urgent Care Network. *Pediatrics*. 2017;139(4):e20162103. doi:10.1542/peds.2016-2103

731. Selekman RE, Allen IE, Copp HL. Determinants of practice patterns in pediatric UTI management. *J Pediatr Urol*. 2016;12(5):308.e1-308.e6. doi:10.1016/j.jpurol.2016.05.036

732. Watson JR, Sánchez PJ, Spencer JD, Cohen DM, Hains DS. Urinary Tract Infection and Antimicrobial Stewardship in the Emergency Department. *Pediatr Emer Care*. 2018;34(2):93-95. doi:10.1097/PEC.0000000000000688

733. Doern CD, Richardson SE. Diagnosis of Urinary Tract Infections in Children. *J Clin Microbiol*. 2016;54(9):2233-2242. doi:10.1128/JCM.00189-16

734. Kim GA, Koo JW. Validity of bag urine culture for predicting urinary tract infections in febrile infants: a paired comparison of urine collection methods. *Korean J Pediatr*. 2015;58(5):183-189. doi:10.3345/kjp.2015.58.5.183

735. Hay AD, Birnie K, Busby J, et al. 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. *Health Technol Assess*. 2016;20(51):1-294. doi:10.3310/hta20510

736. Lee MM, Briars L, Ohler KH, Gross A, Oliveri LM. Evaluation of Outpatient Antibiotic Prescribing for Urinary Tract Infection in Pediatric Patients Ages 2 Months to 18 Years. *J Pediatr Pharmacol Ther*. 2023;28(3):241-246. doi:10.5863/1551-6776-28.3.241

737. Butler CC, O'Brien K, Pickles T, et al. Childhood urinary tract infection in primary care: a prospective observational study of prevalence, diagnosis, treatment, and recovery. *Br J Gen Pract*. 2015;65(633):e217-223. doi:10.3399/bjgp15X684361

738. Shaikh N, Hoberman A, Hum SW, et al. Development and Validation of a Calculator for Estimating the Probability of Urinary Tract Infection in Young Febrile Children. *JAMA Pediatr*. 2018;172(6):550-556. doi:10.1001/jamapediatrics.2018.0217

739. Velasco R, Benito H, Mozun R, et al. Importance of Urine Dipstick in Evaluation of Young Febrile Infants With Positive Urine Culture: A Spanish Pediatric Emergency Research Group Study. *Pediatr Emer Care*. 2016;32(12):851-855. doi:10.1097/PEC.0000000000000935

740. Suresh J, Krishnamurthy S, Mandal J, Mondal N, Sivamurukan P. Diagnostic Accuracy of Point-of-care Nitrite and Leukocyte Esterase Dipstick Test for the Screening of Pediatric Urinary Tract Infections. *Saudi J Kidney Dis Transpl*. 2021;32(3):703. doi:10.4103/1319-2442.336765

741. Nadeem S, Badawy M, Oke OK, Filkins LM, Park JY, Hennes HM. Pyuria and Urine Concentration for Identifying Urinary Tract Infection in Young Children. *Pediatrics*. 2021;147(2):e2020014068. doi:10.1542/peds.2020-014068

742. Chaudhari PP, Monuteaux MC, Bachur RG. Urine Concentration and Pyuria for Identifying UTI in Infants. *Pediatrics*. 2016;138(5):e20162370. doi:10.1542/peds.2016-2370

743. Yavaş DP, Arslansoyu Çamlar S, Soylu A, Kavukçu S. Clinical predictive value of the urine leukocyte esterase test positivity in childhood. *Pediatrics International*. 2021;63(11):1334-1338. doi:10.1111/ped.14643

744. Alonso-Cadenas JA, Sancosmed Ron M, Herrero B, et al. Role of urine culture in paediatric patients with cancer with fever and neutropenia: a prospective observational study. *Arch Dis Child*. Published online August 8, 2023:archdischild-2023-325992. doi:10.1136/archdischild-2023-325992

745. Nadeem S, Manuel MM, Oke OK, et al. Association of Pyuria with Uropathogens in Young Children. *The Journal of Pediatrics*. 2022;245:208-212.e2. doi:10.1016/j.jpeds.2022.01.048

746. Ünsal H, Kaman A, Tanır G. Relationship between urinalysis findings and responsible pathogens in children with urinary tract infections. *J Pediatr Urol*. 2019;15(6):606.e1-606.e6. doi:10.1016/j.jpurol.2019.09.017

747. Azzarone G, Liewehr S, O'Connor K. Cystitis. *Pediatr Rev*. 2007;28(12):474-476. doi:10.1542/pir.28-12-474

748. Raszka WV, Khan O. Pyelonephritis. *Pediatr Rev*. 2005;26(10):364-370. doi:10.1542/pir.26-10-364

749. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary Tract Infection in Children. *Recent Pat Inflamm Allergy Drug Discov*. 2019;13(1):2-18. doi:10.2174/1872213X13666181228154940

750. Živković D, Lukić MS, Živković D, Lukić MS. Cystitis in Children. In: *Cystitis - Updates and Challenges*. IntechOpen; 2023. doi:10.5772/intechopen.111887

751. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med*. 2003;348(3):195-202. doi:10.1056/NEJMoa021698

752. Simões E Silva AC, Oliveira EA, Mak RH. Urinary tract infection in pediatrics: an overview. *J Pediatr (Rio J)*. 2020;96 Suppl 1(Suppl 1):65-79. doi:10.1016/j.jped.2019.10.006

753. Schnadower D, Kuppermann N, Macias CG, et al. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074-1083. doi:10.1542/peds.2010-0479

754. Schnadower D, Kuppermann N, Macias CG, et al. Outpatient Management of Young Febrile Infants With Urinary Tract Infections. *Pediatric Emergency Care*. 2014;30(9):591. doi:10.1097/PEC.0000000000000202

755. Sarvis AB, Sarvis RC, Schnadower D, Chamberlain JM, Mathison DJ. Admit Versus Discharge-A Cost Analysis of Infants 29 to 60 Days Old With Febrile Urinary Tract Infection at Low Risk for Bacteremia. *Acad Pediatr*. 2019;19(2):209-215. doi:10.1016/j.acap.2018.11.002

756. Tullus K, Shaikh N. Urinary tract infections in children. *The Lancet*. 2020;395(10237):1659-1668. doi:10.1016/S0140-6736(20)30676-0

757. Karavanaki K, Koufadaki AM, Soldatou A, et al. Fever duration during treated urinary tract infections and development of permanent renal lesions. *Arch Dis Child*. 2019;104(5):466-470. doi:10.1136/archdischild-2017-314576

758. Massanyi EZ, Preece J, Gupta A, Lin SM, Wang MH. Utility of screening ultrasound after first febrile UTI among patients with clinically significant vesicoureteral reflux. *Urology*. 2013;82(4):905-909. doi:10.1016/j.urology.2013.04.026

759. Nelson CP, Johnson EK, Logvinenko T, Chow JS. Ultrasound as a screening test for genitourinary anomalies in children with UTI. *Pediatrics*. 2014;133(3):e394-403. doi:10.1542/peds.2013-2109

760. Alon US, Ganapathy S. Should renal ultrasonography be done routinely in children with first urinary tract infection? *Clin Pediatr (Phila)*. 1999;38(1):21-25. doi:10.1177/000992289903800103

761. Shaikh N, Spingarn RB, Hum SW. Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. *Cochrane Database Syst Rev*. 2016;7(7):CD010657. doi:10.1002/14651858.CD010657.pub2

762. Jahnukainen T, Honkinen O, Ruuskanen O, Mertsola J. Ultrasonography after the first febrile urinary tract infection in children. *Eur J Pediatr*. 2006;165(8):556-559. doi:10.1007/s00431-006-0113-4

763. Roberts JA. Experimental pyelonephritis in the monkey. III. Pathophysiology of ureteral malfunction induced by bacteria. *Invest Urol*. 1975;13(2):117-120.

764. Battula V, Krupanandan RK, Nambi PS, Ramachandran B. Safety and Feasibility of Antibiotic De-escalation in Critically Ill Children With Sepsis - A Prospective Analytical Study From a Pediatric ICU. *Front Pediatr*. 2021;9:640857. doi:10.3389/fped.2021.640857

765. Ibrahim NA, Bakry MM, Ching SE, Tahir NM, Shah NN. Early Empiric Antibiotic De-escalation in Suspected Early Onset Neonatal Sepsis. *Indian Journal of Pharmaceutical Sciences*. 2019;81(5):913-921.

766. Rungsitsathian K, Wacharachaisurapol N, Nakaranurack C, et al. Acceptance and outcome of interventions in a meropenem de-escalation antimicrobial stewardship program in pediatrics. *Pediatr Int*. 2021;63(12):1458-1465. doi:10.1111/ped.14703

767. Bhullar HS, Shaikh FA, Deepak R, Poddutoor PK, Chirla D. Antimicrobial Justification form for Restricting Antibiotic Use in a Pediatric Intensive Care Unit. *Indian Pediatr*. 2016;53(4):304-306. doi:10.1007/s13312-016-0841-0

768. Renk H, Sarmisak E, Spott C, Kumpf M, Hofbeck M, Hölzl F. Antibiotic stewardship in the PICU: Impact of ward rounds led by paediatric infectious diseases specialists on antibiotic consumption. *Sci Rep*. 2020;10:8826. doi:10.1038/s41598-020-65671-0

769. Mantadakis E, Kopsidas I, Coffin S, et al. A national study of antibiotic use in Greek pediatric hematology oncology and bone marrow transplant units. *Antimicrob Steward Healthc Epidemiol*. 2022;2(1):e71. doi:10.1017/ash.2022.43

770. Antonio MEE, Cassandra BGC, Emiliano RJD, et al. Treatment of asymptomatic bacteriuria in the first 2 months after kidney transplant: A controlled clinical trial. *Transplant Infectious Disease*. 2022;24(6):e13934. doi:10.1111/tid.13934

771. Alexopoulos E, Memmos D, Sakellariou G, Paschalidou E, Kyrou A, Papadimitriou M. Urinary tract infections after renal transplantation. *Drugs Exp Clin Res*. 1985;11(2):101-105.

772. Khosravi AD, Abasi Montazeri E, Ghorbani A, Parhizgari N. Bacterial urinary tract infection in renal transplant recipients and their antibiotic resistance pattern: A four-year study. *Iran J Microbiol*. 2014;6(2):74-78.

773. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation*. 2019;33(9):e13507. doi:10.1111/ctr.13507

774. Coussement J, Kamar N, Matignon M, et al. Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial. *Clinical Microbiology and Infection*. 2021;27(3):398-405. doi:10.1016/j.cmi.2020.09.005

775. Sabé N, Oriol I, Melilli E, et al. Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial. *Open Forum Infect Dis*. 2019;6(6):ofz243. doi:10.1093/ofid/ofz243

776. Origüen J, López-Medrano F, Fernández-Ruiz M, et al. Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial. *American Journal of Transplantation*. 2016;16(10):2943-2953. doi:10.1111/ajt.13829

777. Amano M, Shimizu T. Emphysematous cystitis: a review of the literature. *Intern Med*. 2014;53(2):79-82. doi:10.2169/internalmedicine.53.1121

778. Wu SY, Yang SSD, Chang SJ, Hsu CK. Emphysematous pyelonephritis: classification, management, and prognosis. *Tzu Chi Med J*. 2022;34(3):297-302. doi:10.4103/tcmj.tcmj_257_21

779. Somani BK, Nabi G, Thorpe P, Hussey J, Cook J, N'Dow J. Is Percutaneous Drainage the New Gold Standard in the Management of Emphysematous Pyelonephritis? Evidence From a Systematic Review. *The Journal of Urology*. 2008;179(5):1844-1849. doi:10.1016/j.juro.2008.01.019

780. Thomas AA, Lane BR, Thomas AZ, Remer EM, Campbell SC, Shoskes DA. Emphysematous cystitis: a review of 135 cases. *BJU Int*. 2007;100(1):17-20. doi:10.1111/j.1464-410X.2007.06930.x

781. Grupper M, Kravtsov A, Potasman I. Emphysematous cystitis: illustrative case report and review of the literature. *Medicine (Baltimore)*. 2007;86(1):47-53. doi:10.1097/MD.0b013e3180307c3a

782. Mokabberi R, Ravakhah K. Emphysematous urinary tract infections: diagnosis, treatment and survival (case review series). *Am J Med Sci*. 2007;333(2):111-116. doi:10.1097/00000441-200702000-00009

783. Ubee SS, McGlynn L, Fordham M. Emphysematous pyelonephritis: EMPHYSEMATOUS PYELONEPHRITIS. *BJU International*. 2011;107(9):1474-1478. doi:10.1111/j.1464-410X.2010.09660.x

784. Bjurlin MA, Hurley SD, Kim DY, et al. Clinical Outcomes of Nonoperative Management in Emphysematous Urinary Tract Infections. *Urology*. 2012;79(6):1281-1285. doi:10.1016/j.urology.2012.02.023

785. Quint HJ, Drach GW, Rappaport WD, Hoffmann CJ. Emphysematous Cystitis: A Review of the Spectrum of Disease. *Journal of Urology*. 1992;147(1):134-137. doi:10.1016/S0022-5347(17)37160-4

786. Aboumarzouk OM, Hughes O, Narahari K, et al. Emphysematous pyelonephritis: Time for a management plan with an evidence-based approach. *Arab Journal of Urology*. 2014;12(2):106-115. doi:10.1016/j.aju.2013.09.005

787. Koch GE, Johnsen NV. The Diagnosis and Management of Life-threatening Urologic Infections. *Urology*. 2021;156:6-15. doi:10.1016/j.urology.2021.05.011

788. Rubilotta E, Balzarro M, Lacola V, Sarti A, Porcaro AB, Artibani W. Current clinical management of renal and perinephric abscesses: a literature review. *Urologia*. 2014;81(3):144-147. doi:10.5301/urologia.5000044

789. Lee SH, Jung HJ, Mah SY, Chung BH. Renal abscesses measuring 5 cm or less: outcome of medical treatment without therapeutic drainage. *Yonsei Med J*. 2010;51(4):569-573. doi:10.3349/ymj.2010.51.4.569

790. Siegel JF, Smith A, Moldwin R. Minimally invasive treatment of renal abscess. *J Urol*. 1996;155(1):52-55.

791. Shu T, Green JM, Orihuela E. Renal and perirenal abscesses in patients with otherwise anatomically normal urinary tracts. *J Urol*. 2004;172(1):148-150. doi:10.1097/01.ju.0000132140.48587.b8

792. Meng MV, Mario LA, McAninch JW. Current treatment and outcomes of perinephric abscesses. *J Urol*. 2002;168(4 Pt 1):1337-1340. doi:10.1016/S0022-5347(05)64443-6

793. Coelho RF, Schneider-Monteiro ED, Mesquita JLB, Mazzucchi E, Marmo Lucon A, Srougi M. Renal and perinephric abscesses: analysis of 65 consecutive cases. *World J Surg*. 2007;31(2):431-436. doi:10.1007/s00268-006-0162-x

794. Rai R, Karan S, Kayastha A. Renal and Perinephric Abscesses Revisited. *Medical Journal Armed Forces India*. 2007;63(3):223-225. doi:10.1016/S0377-1237(07)80139-0

795. Lin HS, Ye JJ, Huang TY, Huang PY, Wu TS, Lee MH. Characteristics and factors influencing treatment outcome of renal and perinephric abscess--a 5-year experience at a tertiary teaching hospital in Taiwan. *J Microbiol Immunol Infect*. 2008;41(4):342-350.

796. Gardiner RA, Gwynne RA, Roberts SA. Perinephric abscess. *BJU Int*. 2011;107 Suppl 3:20-23. doi:10.1111/j.1464-410X.2011.10050.x

797. Lee BE, Seol HY, Kim TK, et al. Recent clinical overview of renal and perirenal abscesses in 56 consecutive cases. *Korean J Intern Med*. 2008;23(3):140-148. doi:10.3904/kjim.2008.23.3.140

798. Hutchison FN, Kaysen GA. Perinephric abscess: the missed diagnosis. *Med Clin North Am*. 1988;72(5):993-1014. doi:10.1016/s0025-7125(16)30726-x

799. Sheinfeld J, Erturk E, Spataro RF, Cockett AT. Perinephric abscess: current concepts. *J Urol*. 1987;137(2):191-194. doi:10.1016/s0022-5347(17)43946-2

800. Liu XQ, Wang CC, Liu YB, Liu K. Renal and perinephric abscesses in West China Hospital: 10-year retrospective-descriptive study. *World J Nephrol*. 2016;5(1):108-114. doi:10.5527/wjn.v5.i1.108

801. Saiki J, Vaziri ND, Barton C. Perinephric and intranephric abscesses: a review of the literature. *West J Med*. 1982;136(2):95-102.

802. Okafor CN, Onyeaso EE. Perinephric Abscess. In: *StatPearls*. StatPearls Publishing; 2023. Accessed November 29, 2023. http://www.ncbi.nlm.nih.gov/books/NBK536936/

803. Demertzis J, Menias CO. State of the art: imaging of renal infections. *Emerg Radiol*. 2007;14(1):13-22. doi:10.1007/s10140-007-0591-3

804. Patel H, Shekar Paulraj A, Anand B. Thinking of Draining a Renal Abscess? Wait! - Could Be Acute Lobar Nephronia. *Urology*. 2021;156:e90-e92. doi:10.1016/j.urology.2021.07.008

805. M E, P C, L S, et al. Acute bacterial prostatitis: heterogeneity in diagnostic criteria and management. Retrospective multicentric analysis of 371 patients diagnosed with acute prostatitis. *BMC infectious diseases*. 2008;8. doi:10.1186/1471-2334-8-12

806. McNaughton Collins M, Fowler FJ, Elliott DB, Albertsen PC, Barry MJ. Diagnosing and treating chronic prostatitis: do urologists use the four-glass test? *Urology*. 2000;55(3):403-407. doi:10.1016/s0090-4295(99)00536-1

807. Gamé X, Vincendeau S, Palascak R, Milcent S, Fournier R, Houlgatte A. Total and free serum prostate specific antigen levels during the first month of acute prostatitis. *Eur Urol*. 2003;43(6):702-705. doi:10.1016/s0302-2838(03)00158-1

808. Gill BC, Shoskes DA. Bacterial prostatitis. *Curr Opin Infect Dis*. 2016;29(1):86-91. doi:10.1097/QCO.0000000000000222

809. Krieger JN, Nyberg L, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236-237. doi:10.1001/jama.282.3.236

810. de la Rosette JJ, Hubregtse MR, Meuleman EJ, Stolk-Engelaar MV, Debruyne FM. Diagnosis and treatment of 409 patients with prostatitis syndromes. *Urology*. 1993;41(4):301-307. doi:10.1016/0090-4295(93)90584-w

811. Millán-Rodríguez F, Palou J, Bujons-Tur A, et al. Acute bacterial prostatitis: two different subcategories according to a previous manipulation of the lower urinary tract. *World J Urol*. 2006;24(1):45-50. doi:10.1007/s00345-005-0040-4

812. Marquez-Algaba E, Pigrau C, Bosch-Nicolau P, et al. Risk Factors for Relapse in Acute Bacterial Prostatitis: the Impact of Antibiotic Regimens. *Microbiol Spectr*. 2021;9(2):e0053421. doi:10.1128/Spectrum.00534-21

813. Yoon BI, Han DS, Ha US, et al. Clinical courses following acute bacterial prostatitis. *Prostate Int*. 2013;1(2):89-93. doi:10.12954/PI.12013

814. Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes. *JAMA Internal Medicine*. 2013;173(1):62-68. doi:10.1001/2013.jamainternmed.829

815. Etienne M, Pestel-Caron M, Chavanet P, Caron F. Performance of the urine leukocyte esterase and nitrite dipstick test for the diagnosis of acute prostatitis. *Clin Infect Dis*. 2008;46(6):951-953; author reply 953. doi:10.1086/528873

816. Trauzzi SJ, Kay CJ, Kaufman DG, Lowe FC. Management of prostatic abscess in patients with human immunodeficiency syndrome. *Urology*. 1994;43(5):629-633. doi:10.1016/0090-4295(94)90176-7

817. Ludwig M, Schroeder-Printzen I, Schiefer HG, Weidner W. Diagnosis and therapeutic management of 18 patients with prostatic abscess. *Urology*. 1999;53(2):340-345. doi:10.1016/s0090-4295(98)00503-2

818. Horcajada JP, Vilana R, Moreno-Martínez A, et al. Transrectal prostatic ultrasonography in acute bacterial prostatitis: findings and clinical implications. *Scand J Infect Dis*. 2003;35(2):114-120. doi:10.1080/0036554021000027018

819. Kravchick S, Cytron S, Agulansky L, Ben-Dor D. Acute prostatitis in middle-aged men: a prospective study. *BJU International*. 2004;93(1):93-96. doi:10.1111/j.1464-410X.2004.04642.x

820. Cho IR, Lee KC, Lee SE, et al. Clinical outcome of acute bacterial prostatistis, a multicenter study. *Korean Journal of Urology*. 2005;46(10):1034-1039.

821. Pricop C. LEVOFLOXACIN VERSUS CEFIXIME AS AN EMPIRIC TREATMENT IN ACUTE BACTERIAL PROSTATITIS. *FARMACIA*. 2021;69(4):682-687. doi:10.31925/farmacia.2021.4.7

822. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis*. 2010;50(12):1641-1652. doi:10.1086/652861

823. Magri V, Montanari E, Marras E, Perletti G. Aminoglycoside antibiotics for NIH category II chronic bacterial prostatitis: A single-cohort study with one-year follow-up. *Exp Ther Med*. 2016;12(4):2585-2593. doi:10.3892/etm.2016.3631

824. Takasaki N, Ra S, Okada S, et al. Transference of antibiotics into prostatic tissues: sampling method by transurethral resection for the measurement of the concentration of antibiotics in prostatic tissue. *Hinyokika Kiyo*. 1986;32(7):969-975.

825. Shrestha N, Amuh D, Goldman M, Riebel W, Tomford J. Treatment of a Complicated Vancomycin-Resistant Enterococcal Urinary Tract Infection with Fosfomycin. *Infectious Diseases in Clinical Practice*. 2000;9:368-371. doi:10.1097/00019048-200009090-00004

826. Pitout JDD. Enterobacteriaceae that produce extended-spectrum β-lactamases and AmpC β-lactamases in the community: the tip of the iceberg? *Curr Pharm Des*. 2013;19(2):257-263.

827. Roberts MJ, Williamson DA, Hadway P, Doi SAR, Gardiner RA, Paterson DL. Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: A bias-adjusted meta-analysis. *Int J Antimicrob Agents*. 2014;43(4):301-309. doi:10.1016/j.ijantimicag.2014.01.008

828. Gleckman R, Crowley M, Natsios GA. Therapy of Recurrent Invasive Urinary-Tract Infections of Men. *N Engl J Med*. 1979;301(16):878-880. doi:10.1056/NEJM197910183011607

829. Smith JW, Jones SR, Reed WP, Tice AD, Deupree RH, Kaijser B. Recurrent urinary tract infections in men. Characteristics and response to therapy. *Ann Intern Med*. 1979;91(4):544-548. doi:10.7326/0003-4819-91-4-544

830. Stamey T. Prostatitis. 1981;74(1). doi:https://doi.org/10.1177/014107688107400106

831. Nickel JC, Shoskes D, Wang Y, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? *J Urol*. 2006;176(1):119-124. doi:10.1016/S0022-5347(06)00498-8

832. Schaeffer AJ, Wu SC, Tennenberg AM, Kahn JB. Treatment of chronic bacterial prostatitis with levofloxacin and ciprofloxacin lowers serum prostate specific antigen. *J Urol*. 2005;174(1):161-164. doi:10.1097/01.ju.0000162017.24965.2b

833. Bradshaw AW, Pe M, Bechis SK, et al. Antibiotics are not necessary during routine cystoscopic stent removal: A randomized controlled trial at UC San Diego. *Urol Ann*. 2020;12(4):373-378. doi:10.4103/UA.UA_130_19

834. Westhoff N, Anokhin A, Patroi P, Neuberger M, Siegel F, Pfalzgraf D. Prospective Evaluation of Antibiotic Management in Ureteral Stent and Nephrostomy Interventions. *Urol Int*. 2022;106(4):411-418. doi:10.1159/000517546

835. Yang C, Wei H, Zhan H, et al. Effect of preoperative prophylactic antibiotic use on postoperative infection after percutaneous nephrolithotomy in patients with negative urine culture: a single-center randomized controlled trial. *World J Urol*. Published online October 7, 2023. doi:10.1007/s00345-023-04623-5

836. Darenkov AF, Derevianko II, Martov AG, Kotliarova GA, Kondrat'eva EM, Siniukhin VN. [The prevention of infectious-inflammatory complications in the postoperative period in percutaneous surgical interventions in patients with urolithiasis]. *Urol Nefrol (Mosk)*. 1994;(2):24-26.

837. Jung HD, Cho KS, Moon YJ, Chung DY, Kang DH, Lee JY. Antibiotic prophylaxis for percutaneous nephrolithotomy: An updated systematic review and meta-analysis. *PLoS One*. 2022;17(4):e0267233. doi:10.1371/journal.pone.0267233

838. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256. doi:10.1097/01.CCM.0000050454.01978.3B

839. Bag S, Kumar S, Taneja N, Sharma V, Mandal AK, Singh SK. One week of nitrofurantoin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *Urology*. 2011;77(1):45-49. doi:10.1016/j.urology.2010.03.025

840. Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *BJU Int*. 2006;98(5):1075-1079. doi:10.1111/j.1464-410X.2006.06450.x

841. Gravas S, Montanari E, Geavlete P, et al. Postoperative infection rates in low risk patients undergoing percutaneous nephrolithotomy with and without antibiotic prophylaxis: a matched case control study. *J Urol*. 2012;188(3):843-847. doi:10.1016/j.juro.2012.05.007

842. Fourcade RO. Antibiotic prophylaxis with cefotaxime in endoscopic extraction of upper urinary tract stones: a randomized study. The Cefotaxime Cooperative Group. *J Antimicrob Chemother*. 1990;26 Suppl A:77-83. doi:10.1093/jac/26.suppl_a.77

843. Doğan HS, Sahin A, Cetinkaya Y, Akdoğan B, Ozden E, Kendi S. Antibiotic prophylaxis in percutaneous nephrolithotomy: prospective study in 81 patients. *J Endourol*. 2002;16(9):649-653. doi:10.1089/089277902761402989

844. Olivero A, Riccardi N, Ndrevataj D, et al. Flexible cystoscopy for ureteral stent removal without antimicrobial prophylaxis. A prospective observational study. *Urologia*. 2021;88(2):130-134. doi:10.1177/0391560320980897

845. Abbott JE, Han A, McDonald M, Lakin C, Sur RL. Are antibiotics necessary during routine cystoscopic stent removal? *Transl Androl Urol*. 2016;5(5):784-788. doi:10.21037/tau.2016.08.13

846. Kar M, Dubey A, Patel SS, Siddiqui T, Ghoshal U, Sahu C. Characteristics of Bacterial Colonization and Urinary Tract Infection after Indwelling of Double-J ureteral Stent and Percutaneous Nephrostomy Tube. *J Glob Infect Dis*. 2022;14(2):75-80. doi:10.4103/jgid.jgid_276_21

847. Lewis A, Lin J, James H, et al. A single-center intervention to discontinue postoperative antibiotics after spinal fusion. *Br J Neurosurg*. 2018;32(2):177-181. doi:10.1080/02688697.2017.1396284

848. Takemoto RC, Lonner B, Andres T, et al. Appropriateness of Twenty-four-Hour Antibiotic Prophylaxis After Spinal Surgery in Which a Drain Is Utilized: A Prospective Randomized Study. *J Bone Joint Surg Am*. 2015;97(12):979-986. doi:10.2106/JBJS.L.00782

849. Geraghty RM, Pietropaolo A, Villa L, et al. Post-Ureteroscopy Infections Are Linked to Pre-Operative Stent Dwell Time over Two Months: Outcomes of Three European Endourology Centres. *J Clin Med*. 2022;11(2):310. doi:10.3390/jcm11020310

850. Wang Y, Yang Y, Zhang H, Wang Y. Early Removal of Ureteral Stent After Kidney Transplant Could Decrease Incidence of Urinary Tract Infection: A Systematic Review and Meta-Analysis. *Exp Clin Transplant*. 2022;20(1):28-34. doi:10.6002/ect.2021.0183

851. Arabi Z, Al Thiab K, Altheaby A, et al. The Impact of Timing of Stent Removal on the Incidence of UTI, Recurrence, Symptomatology, Resistance, and Hospitalization in Renal Transplant Recipients. *J Transplant*. 2021;2021:3428260. doi:10.1155/2021/3428260

852. Kaliyeva S, Simokhina N, Lavrinenko A, et al. Bacterial Colonization Incidence before and after Indwelling Double-J Ureteral Stents. *Antibiotics (Basel)*. 2022;11(7):850. doi:10.3390/antibiotics11070850

853. Salari B, Khalid M, Ivan S, et al. Urine versus stent cultures and clinical UTIs. *Int Urol Nephrol*. 2021;53(11):2237-2242. doi:10.1007/s11255-021-02964-x

854. Vallée M, Bey E, Bouiller K, et al. Epidemiology and risk factors for ureteral stent-associated urinary tract infections in non-transplanted renal patients: a systematic review of the literature. *World J Urol*. 2021;39(10):3845-3860. doi:10.1007/s00345-021-03693-7

855. Kim JY, Yeo JK, Park MG, Sung LH, Cho DY, Yu JH. Determination of microbiological characteristics and risk factors associated with bacteriuria and symptomatic urinary tract infection in patients with retained ureteral stents: an observational study. *Transl Androl Urol*. 2023;12(1):19-32. doi:10.21037/tau-22-331

856. Szvalb AD, El Haddad H, Rolston KV, et al. Risk factors for recurrent percutaneous nephrostomy catheter-related infections. *Infection*. 2019;47(2):239-245. doi:10.1007/s15010-018-1245-y

857. Mert D, Iskender G, Kolgelier S, Ertek M. Evaluation of risk factors, causative pathogens, and treatment in recurrent percutaneous nephrostomy catheter-related urinary tract infections in cancer patients. *Medicine (Baltimore)*. 2023;102(14):e33002. doi:10.1097/MD.0000000000033002

858. Dede G, Deveci Ö, Dede O, et al. For reliable urine cultures in the detection of complicated urinary tract infection, do we use urine specimens obtained with urethral catheter or a nephrostomy tube? *Turk J Urol*. 2016;42(4):290-294. doi:10.5152/tud.2016.00947

859. Batura D, Gopal Rao G. A systematic review of the clinical significance of nephrostomy urine cultures. *World J Urol*. 2020;38(1):45-55. doi:10.1007/s00345-019-02663-4

860. Fisher JF, Sobel JD, Kauffman CA, Newman CA. Candida Urinary Tract Infections—Treatment. *Clinical Infectious Diseases*. 2011;52(suppl_6):S457-S466. doi:10.1093/cid/cir112

861. Mathers MJ, Lazica DA, Roth S. [Non-bacterial cystitis: principles, diagnostics and etiogenic therapy options]. *Aktuelle Urol*. 2010;41(6):361-368. doi:10.1055/s-0030-1262615

862. Luciani LG, Mattevi D. Urinary Tract Infections: Virus. *Encyclopedia of Infection and Immunity*. Published online 2022:32-43. doi:10.1016/B978-0-12-818731-9.00139-7

863. Hirsch HH. BK virus: opportunity makes a pathogen. *Clin Infect Dis*. 2005;41(3):354-360. doi:10.1086/431488

864. Allen CW, Alexander SI. Adenovirus associated haematuria. *Arch Dis Child*. 2005;90(3):305-306. doi:10.1136/adc.2003.037952

865. Bouza E, San Juan R, Muñoz P, Voss A, Kluytmans J, Co-operative Group of the European Study Group on Nosocomial Infections. A European perspective on nosocomial urinary tract infections I. Report on the microbiology workload, etiology and antimicrobial susceptibility (ESGNI-003 study). European Study Group on Nosocomial Infections. *Clin Microbiol Infect*. 2001;7(10):523-531. doi:10.1046/j.1198-743x.2001.00326.x

866. Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis*. 2000;30(1):19-24. doi:10.1086/313580

867. Guler S, Ural O, Findik D, Arslan U. Risk factors for nosocomial candiduria. *Saudi Med J*. 2006;27(11):1706-1710.

868. Jacobs DM, Dilworth TJ, Beyda ND, Casapao AM, Bowers DR. Overtreatment of Asymptomatic Candiduria among Hospitalized Patients: a Multi-institutional Study. *Antimicrob Agents Chemother*. 2017;62(1):e01464-17. doi:10.1128/AAC.01464-17

869. Erden A, Fitoz S, Karagülle T, Tükel S, Akyar S. Radiological findings in the diagnosis of genitourinary candidiasis. *Pediatr Radiol*. 2000;30(12):875-877. doi:10.1007/s002470000351

870. Wise GJ, Shteynshlyuger A. How to diagnose and treat fungal infections in chronic prostatitis. *Curr Urol Rep*. 2006;7(4):320-328. doi:10.1007/s11934-996-0012-2

871. Wen SC, Juan YS, Wang CJ, et al. Emphysematous prostatic abscess: case series study and review. *Int J Infect Dis*. 2012;16(5):e344-349. doi:10.1016/j.ijid.2012.01.002

872. Jenkin GA, Choo M, Hosking P, Johnson PD. Candidal epididymo-orchitis: case report and review. *Clin Infect Dis*. 1998;26(4):942-945. doi:10.1086/513937

873. Krishnasamy PV, Liby C. Emphysematous pyelonephritis caused by Candida tropicalis. *Am J Med*. 2010;123(4):e7-8. doi:10.1016/j.amjmed.2009.07.024

874. Lagrotteria D, Rotstein C, Lee CH. Treatment of candiduria with micafungin: A case series. *Can J Infect Dis Med Microbiol*. 2007;18(2):149-150. doi:10.1155/2007/768734

875. Gabardi S, Martin S, Sura M, Mohammed A, Golan Y. Micafungin treatment and eradication of candiduria among hospitalized patients. *Int Urol Nephrol*. 2016;48(11):1881-1885. doi:10.1007/s11255-016-1410-0

876. Rkieh L, El Nekidy WS, Alsoud LO, et al. Outcomes of caspofungin use in the treatment of Candida-related urinary tract infections, a case series. *IDCases*. 2022;28:e01510. doi:10.1016/j.idcr.2022.e01510

877. Sobel JD, Bradshaw SK, Lipka CJ, Kartsonis NA. Caspofungin in the treatment of symptomatic candiduria. *Clin Infect Dis*. 2007;44(5):e46-49. doi:10.1086/510432

878. Ekinci F, Yildizdas D, Horoz OO, Ozgur Gundeslioglu O, Alabaz D. Treatment of Candida urinary tract infections with micafungin in children. *Pediatr Int*. 2022;64(1):e15033. doi:10.1111/ped.15033

879. Javorova Rihova Z, Slobodova L, Hrabovska A. Micafungin Is an Efficient Treatment of Multi Drug-Resistant Candida glabrata Urosepsis: A Case Report. *J Fungi (Basel)*. 2021;7(10):800. doi:10.3390/jof7100800

880. Multani A, Subramanian AK, Liu AY. Successful eradication of chronic symptomatic Candida krusei urinary tract infection with increased dose micafungin in a liver and kidney transplant recipient: Case report and review of the literature. *Transpl Infect Dis*. 2019;21(4):e13118. doi:10.1111/tid.13118

881. Rezai MS, Vaezi A, Fakhim H, et al. Successful treatment with caspofungin of candiduria in a child with Wilms tumor; review of literature. *J Mycol Med*. 2017;27(2):261-265. doi:10.1016/j.mycmed.2017.01.006

882. Kane LE, Muzevich KM. Micafungin in the treatment of candiduria: A case series. *Med Mycol Case Rep*. 2016;11:5-8. doi:10.1016/j.mmcr.2016.01.003

883. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-50. doi:10.1093/cid/civ933

884. Fisher JF, Woeltje K, Espinel-Ingroff A, Stanfield J, DiPiro JT. Efficacy of a single intravenous dose of amphotericin B for Candida urinary tract infections: further favorable experience. *Clin Microbiol Infect*. 2003;9(10):1024-1027. doi:10.1046/j.1469-0691.2003.00711.x

885. Krajewski W, Kamińska D, Poterek A, et al. Pathogenicity of BK virus on the urinary system. *Cent European J Urol*. 2020;73(1):94-103. doi:10.5173/ceju.2020.0034

886. Chong S, Antoni M, Macdonald A, Reeves M, Harber M, Magee CN. BK virus: Current understanding of pathogenicity and clinical disease in transplantation. *Rev Med Virol*. 2019;29(4):e2044. doi:10.1002/rmv.2044

887. Bressollette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. *Am J Transplant*. 2005;5(8):1926-1933. doi:10.1111/j.1600-6143.2005.00934.x

888. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. *Nephrol Dial Transplant*. 2015;30(2):209-217. doi:10.1093/ndt/gfu023

889. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK Polyomavirus: Clinical Aspects, Immune Regulation, and Emerging Therapies. *Clin Microbiol Rev*. 2017;30(2):503-528. doi:10.1128/CMR.00074-16

890. Yaghobi R, Ramzi M, Dehghani S. The role of different risk factors in clinical presentation of hemorrhagic cystitis in hematopoietic stem cell transplant recipients. *Transplant Proc*. 2009;41(7):2900-2902. doi:10.1016/j.transproceed.2009.07.060

891. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. *Bone Marrow Transplant*. 2008;41(1):11-18. doi:10.1038/sj.bmt.1705886

892. Coleman DV, Mackenzie EF, Gardner SD, Poulding JM, Amer B, Russell WJ. Human polyomavirus (BK) infection and ureteric stenosis in renal allograft recipients. *J Clin Pathol*. 1978;31(4):338-347. doi:10.1136/jcp.31.4.338

893. Rajpoot DK, Gomez A, Tsang W, Shanberg A. Ureteric and urethral stenosis: a complication of BK virus infection in a pediatric renal transplant patient. *Pediatr Transplant*. 2007;11(4):433-435. doi:10.1111/j.1399-3046.2006.00673.x

894. Tognon M, Corallini A, Martini F, Negrini M, Barbanti-Brodano G. Oncogenic transformation by BK virus and association with human tumors. *Oncogene*. 2003;22(33):5192-5200. doi:10.1038/sj.onc.1206550

895. Alexiev BA, Randhawa P, Vazquez Martul E, et al. BK virus-associated urinary bladder carcinoma in transplant recipients: report of 2 cases, review of the literature, and proposed pathogenetic model. *Hum Pathol*. 2013;44(5):908-917. doi:10.1016/j.humpath.2012.09.019

896. Oikawa M, Hatakeyama S, Fujita T, et al. BK virus-associated urothelial carcinoma of a ureter graft in a renal transplant recipient: a case report. *Transplant Proc*. 2014;46(2):616-619. doi:10.1016/j.transproceed.2013.09.037

897. Florescu MC, Miles CD, Florescu DF. What do we know about adenovirus in renal transplantation? *Nephrol Dial Transplant*. 2013;28(8):2003-2010. doi:10.1093/ndt/gft036

898. Fanourgiakis P, Georgala A, Vekemans M, et al. Intravesical instillation of cidofovir in the treatment of hemorrhagic cystitis caused by adenovirus type 11 in a bone marrow transplant recipient. *Clin Infect Dis*. 2005;40(1):199-201. doi:10.1086/426594

899. Shimizu T, Kondo T, Matsumoto K, Hishizawa M, Yamashita K, Takaori-Kondo A. Neutropenia and renal dysfunction due to intravesical cidofovir for virus-associated hemorrhagic cystitis after kidney and allogenic hematopoietic stem cell transplantations. *Transpl Infect Dis*. 2019;21(6):e13185. doi:10.1111/tid.13185

900. Keswani M, Moudgil A. Adenovirus-associated hemorrhagic cystitis in a pediatric renal transplant recipient. *Pediatr Transplant*. 2007;11(5):568-571. doi:10.1111/j.1399-3046.2007.00736.x

901. Sakurada M, Kondo T, Umeda M, Kawabata H, Yamashita K, Takaori-Kondo A. Successful treatment with intravesical cidofovir for virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: A case report and a review of the literature. *J Infect Chemother*. 2016;22(7):495-500. doi:10.1016/j.jiac.2016.01.013

902. Gorczynska E, Turkiewicz D, Rybka K, et al. Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2005;11(10):797-804. doi:10.1016/j.bbmt.2005.06.007

903. Hatakeyama N, Suzuki N, Kudoh T, Hori T, Mizue N, Tsutsumi H. Successful cidofovir treatment of adenovirus-associated hemorrhagic cystitis and renal dysfunction after allogenic bone marrow transplant. *Pediatr Infect Dis J*. 2003;22(10):928-929. doi:10.1097/01.inf.0000091399.29505.21

904. Cassano WF. Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1991;7(3):247-248.

905. Jurado M, Navarro JM, Hernández J, Molina MA, DePablos JM. Adenovirus-associated haemorrhagic cystitis after bone marrow transplantation successfully treated with intravenous ribavirin. *Bone Marrow Transplant*. 1995;15(4):651-652.

906. Murphy GF, Wood DP, McRoberts JW, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. *J Urol*. 1993;149(3):565-566. doi:10.1016/s0022-5347(17)36149-9

907. Miyamura K, Hamaguchi M, Taji H, et al. Successful ribavirin therapy for severe adenovirus hemorrhagic cystitis after allogeneic marrow transplant from close HLA donors rather than distant donors. *Bone Marrow Transplant*. 2000;25(5):545-548. doi:10.1038/sj.bmt.1702195

908. Abe S, Miyamura K, Oba T, et al. Oral ribavirin for severe adenovirus infection after allogeneic marrow transplantation. *Bone Marrow Transplant*. 2003;32(11):1107-1108. doi:10.1038/sj.bmt.1704276

909. Homma M, Inoue Y, Hasegawa Y, Kojima H, Kohda Y. Blood ribavirin concentration in high-dose ribavirin for adenovirus-induced haemorrhagic cystitis - a case report. *J Clin Pharm Ther*. 2008;33(1):75-78. doi:10.1111/j.1365-2710.2008.00874.x

910. Cipe FE, Soygür T, Doğu F, Erdoğan O, Bozdoğan G, Ikincioğullari A. Late onset hemorrhagic cystitis in a hematopoietic stem cell recipient: treatment with intravesical hyaluronic acid. *Pediatr Transplant*. 2010;14(6):E79-82. doi:10.1111/j.1399-3046.2009.01169.x

911. Hosokawa K, Aoki G, Ohata K, et al. Effectiveness of hyperbaric oxygen therapy for virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. *Int J Hematol*. 2021;114(1):109-115. doi:10.1007/s12185-021-03120-y

912. Egan J, Vranic G, Ghasemian SR. Alum irrigation for the treatment of adenovirus induced hemorrhagic cystitis in a kidney transplant recipient. *Urol Case Rep*. 2020;30:101042. doi:10.1016/j.eucr.2019.101042

913. Chen FE, Liang RH, Lo JY, Yuen KY, Chan TK, Peiris M. Treatment of adenovirus-associated haemorrhagic cystitis with ganciclovir. *Bone Marrow Transplant*. 1997;20(11):997-999. doi:10.1038/sj.bmt.1700997

914. Painter W, Robertson A, Trost LC, Godkin S, Lampert B, Painter G. First pharmacokinetic and safety study in humans of the novel lipid antiviral conjugate CMX001, a broad-spectrum oral drug active against double-stranded DNA viruses. *Antimicrob Agents Chemother*. 2012;56(5):2726-2734. doi:10.1128/AAC.05983-11

eTable 1. Overview of author selection and section assignments				
Guideline co-chairs: Zachary Nelson, PharmD, MPH, BCIDP, AAHIVP (first author) Alfredo J Mena Lora, MD, FIDSA(senior author)				
Section 1	**Section 2**	**Section 3**	**Section 4**	**Section 5**
Section Leads **1.Susan Egbert** **2. Michelle Blyth**	*Section Leads* **1. Fernando Dominguez** **2. Tina Khadem**	*Section Leads* **1. Nathan P. Beahm** **2. Katie Olney**	*Section Leads* **1. Alexandra Hanretty** **2. Abdullah Tarık Aslan**	*Section Leads* **1.Susan Egbert** **2. Matthew Cappiello**
1. Minji Kang 2. Margaret Fitzpatrick 3. Souradeep Chowdhury 4. Michael Bosco 5. Veronica Zafonte 6. Michael Veve 7. Molly Fleece 8. Daniela de Lima 10. Cihan Papan 11. Fergus Hamilton 12. Bassam Ghanem 13. Sarah Kurz 14. Philipp Jent 15. Dhara Mehta 16. Danielle Casaus 17. Emily G. McDonald 18. Todd C. Lee	1. Minji Kang 2. Mariana Barosa 3. Brad Spellberg 6. Justin Moore 7. Robert M Taylor 8. Boris Jegorović 9. Cihan Papan 10. Emily G. McDonald 11. Todd C. Lee 12. Gloria Aggrey 15. James Wilson (#8) 18. Mira Maximos	1. Alyssa Christensen 6. Brad Spellberg 7. Elias Chahine 8. Daniel Anderson 9. Geena Kludjian 10. Emily G. McDonald 11. Todd C. Lee 15. Alberto Enrico Maraolo	2. Daniel Anderson 4. Cynthia Nguyen 5. Katie Olney 7. Margaret Fitzpatrick 8. Nathan P. Beahm 11. Emily Fox 12. Brad Spellberg 13. Justin Moore 14. Geena Kludjian 15. Emily G. McDonald 16. Todd C. Lee 17. Bassam Ghanem 19. Alberto Enrico Maraolo 23. Ahmed Abdul-Azim 24. Rodolfo Jimenez-Juarez 25. Timothy Li 26. Dhara Mehta	1. Katie Olney 2. Emily Fox 3. Akshatha Ravindra 4. Mira Maximos 5.Fergus Hamilton 6. Mariana Barosa 7. Abdullah Tarık Aslan 8. Emily G. McDonald 9. Brent Footer 10. Bassam Ghanem 11. Annie Joseph 14. Philipp Jent 15. James Wilson 16. Justin Hayes 17. Arsheena Yassin 18. Alexis Thumann 22. Todd C. Lee

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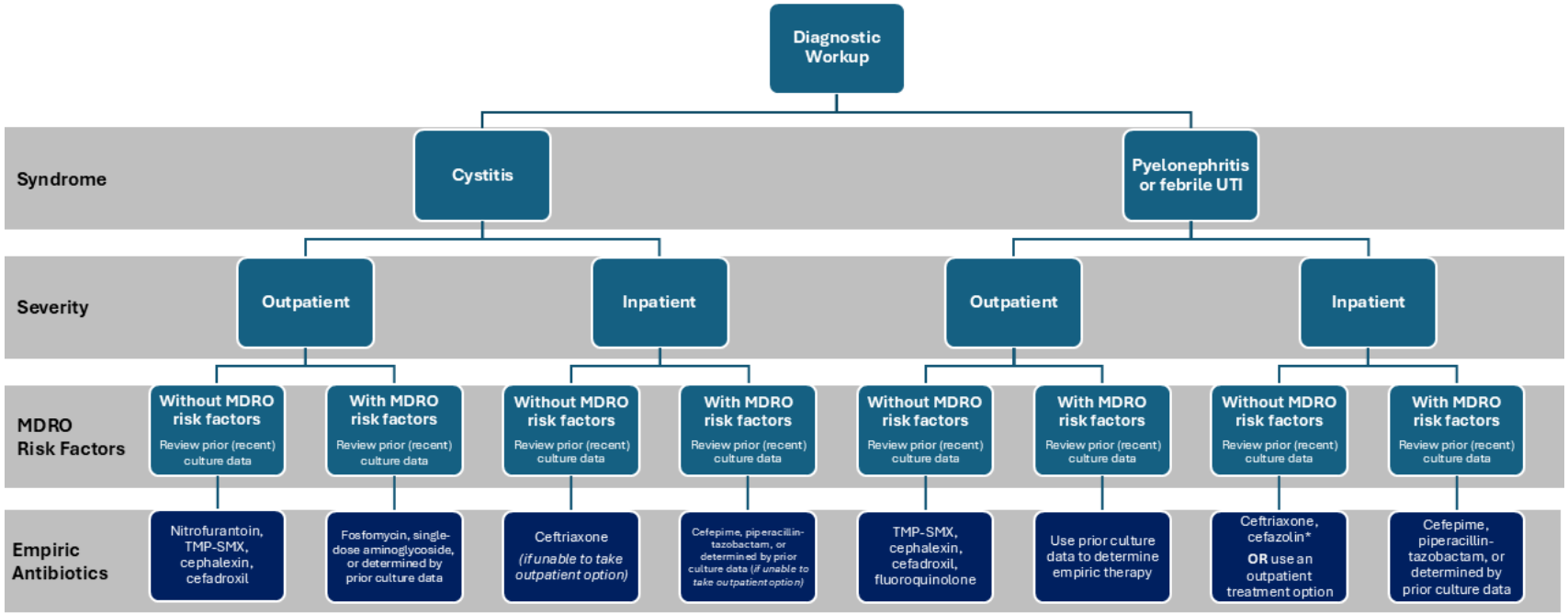
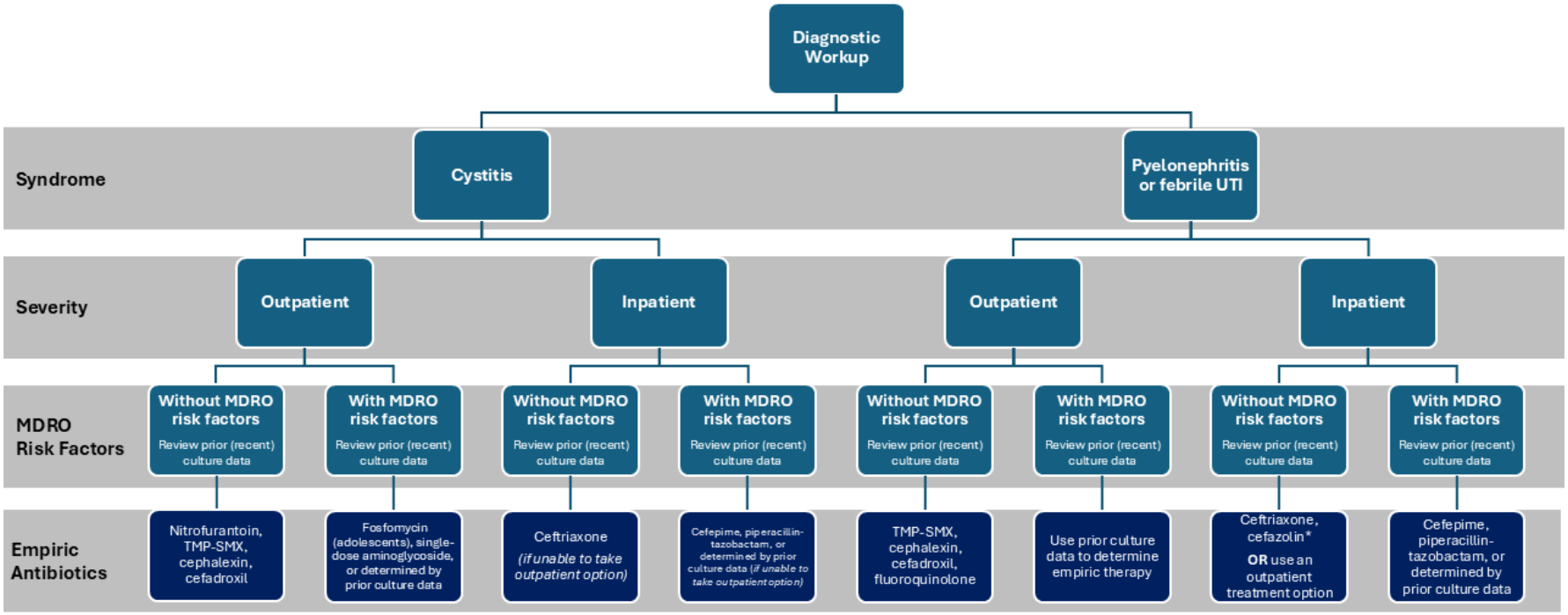
eFigure 1: Empiric Treatment Assessment Framework for Adults



*Cefazolin is a reasonable empiric parenteral option if local resistance rates for *Escherichia coli* are favorable

eFigure 2: Empiric Treatment Assessment Framework for Pediatrics



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