Clinical Practice Guideline by Infectious Diseases Society of America (IDSA): 2025 Guideline on Management and Treatment of Complicated Urinary Tract Infections: Selection of Antibiotic Therapy for Complicated UTI

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A. Initial Selection among Empiric Antibiotic Options for Complicated UTI

B. Stepwise Process to Guide Empiric Antibiotic Choice for Complicated UTI

C. Selection of Definitive Antibiotic Therapy for Complicated UTI

A. Initial Selection among Empiric Antibiotic Options for Complicated UTI

In patients with cUTI, which classes of empiric antibiotic therapy should initially be prioritized?

Recommendations:

I. For patients with **sepsis** due to complicated UTI, we suggest **initially selecting among** the following antibiotics, using the four-step assessment (**Figure 1.1**): third- or fourth-generation cephalosporins, carbapenems, piperacillin-tazobactam, or fluoroquinolones, rather than newer agents (novel beta lactam-beta lactamase inhibitors, cefiderocol, plazomicin) or older aminoglycosides (*conditional recommendation, very low to moderate certainty of evidence*).

Remarks:
-See **Table 1.1** for a more complete list of empiric antibiotic therapy options.
-Please refer to the four-step approach in **Figure 1.1** to choose among these antibiotics for the specific patient (i.e., severity of illness, risk factors for having resistant uropathogen, patient-specific considerations, and antibiogram).
-Agents with broader spectrum of activity against organisms other than Enterobacterales (e.g. *Pseudomonas aeruginosa*, enterococci, or methicillin-resistant *Staphylococcus aureus*) may be considered for patients with sepsis in whom the diagnosis of cUTI is not clear or who are suspected to have cUTI due to these pathogens.

Comments:
-This recommendation places a higher value on providing early, appropriate empiric antibiotic therapy to prevent mortality while deferring stewardship considerations to definitive therapy.
- The certainty of evidence was moderate for all classes of antibiotics, except for third and fourth generation cephalosporins, and older aminoglycosides, for which the certainty of evidence was very low.

II. For patients with suspected complicated UTI without sepsis, we suggest **initially selecting among** the following antibiotics, using the four-step assessment (**Figure 1.1**): third- or fourth-generation cephalosporins, piperacillin-tazobactam, or fluoroquinolones, rather than carbapenems and newer agents (novel beta lactam-beta lactamase inhibitors, cefiderocol, plazomicin) or older aminoglycosides (*conditional recommendation, very low to moderate certainty of evidence*).

Remarks:
-See **Table 1.1** for a more complete list of empiric antibiotic therapy options.
-Please refer to the four-step approach in **Figure 1.1** to choose among these antibiotics for the specific patient (i.e., severity of illness, risk factors for having resistant uropathogen, and patient-specific considerations).
-Other agents (e.g., trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, first or second-generation cephalosporins) are less well studied but may be appropriate in select settings or situations for empiric oral treatment of cUTI.

Comments:
-This recommendation places a higher value on antibiotic stewardship considerations in patients with cUTI who are not septic and in whom the risk of infection-related mortality is

low while also considering costs, resources, and practical aspects of antibiotic administration
-The certainty of evidence was moderate for all classes of antibiotics, except for third and fourth generation cephalosporins and older aminoglycosides, for which the certainty of evidence was very low.

Table 1.1: Potential Empiric Antibiotics for cUTI^ prior to using the four-step approach to choose among these options

Four-Step Approach to choose among these antibiotics: Assess (1) severity of illness, (2) risk factors for resistance, (3) patient-specific considerations, and (4) if septic, consider the antibiogram. See discussion below for details of the four steps.

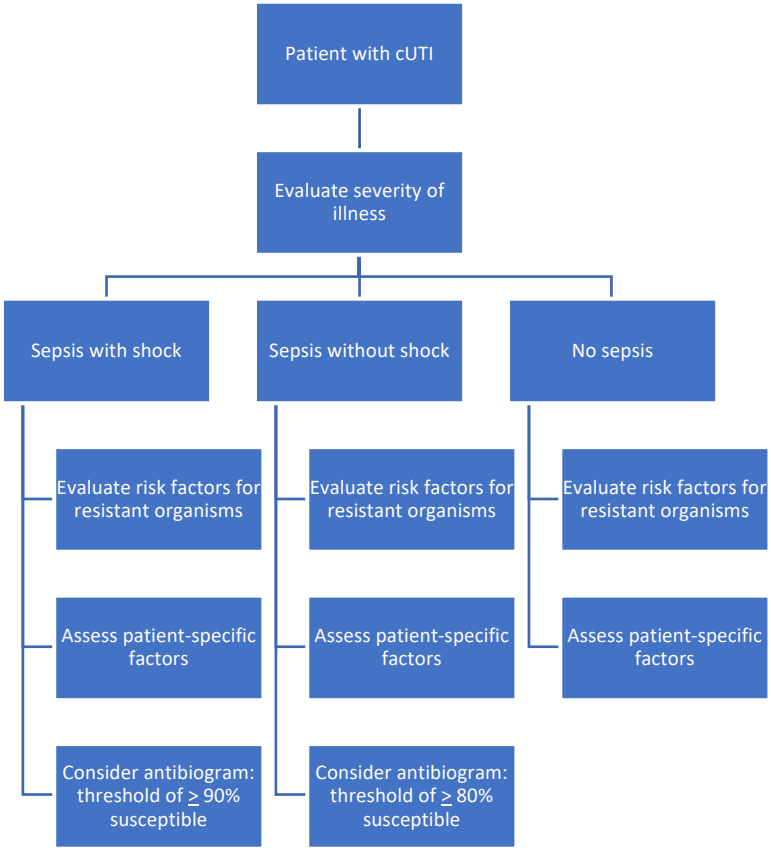
Condition of the Patient	Preferred	Alternative
Sepsis with or without shock**	Third or fourth generation cephalosporins,* carbapenems,# piperacillin-tazobactam, fluoroquinolones&	Novel beta lactam-beta lactamase inhibitors,+ cefiderocol, plazomicin, or older aminoglycosides%
Without sepsis, IV route of therapy	Third or fourth generation cephalosporins,* piperacillin-tazobactam, or fluoroquinolones&	Carbapenems,# newer agents (novel beta lactams-beta lactamase inhibitors,+ cefiderocol, plazomicin), or older aminoglycosides%
Without sepsis, oral route of therapy	Fluoroquinolones& or trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate or oral cephalosporins (see **Table 3.1**)

^Difficult-to-treat resistant pathogens may require use of drugs not listed here (e.g., colistin); refer to IDSA Antimicrobial Resistance guidance.
**Sepsis is life-threatening organ dysfunction related to infection, identified by SOFA score of 2 or higher. Screening tools such as qSOFA or SIRS may be useful for presumptive identification. In sepsis with shock, in step 4 choose an antibiotic for which the susceptibilities of the most relevant organisms are at least 90%. In sepsis without shock, in step 4 choose an antibiotic for which the susceptibilities of the most relevant organisms are at least 80%.
*Third and fourth generation IV cephalosporins include: ceftriaxone, ceftazidime, cefotaxime, and cefepime. (see **Table 2.1 & 3.1**, Dosing of IV and oral antibiotics for cUTI).
&The fluoroquinolones approved for UTI currently include ciprofloxacin and levofloxacin.
#The carbapenems currently include imipenem-cilastatin, doripenem, meropenem, and ertapenem.
+The novel beta lactam-beta lactamase inhibitors currently include ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam.
%Older aminoglycosides include gentamicin, amikacin, and tobramycin.

This table was created in 2025; new drugs approved after this date may also be appropriate choices.

Please note that nitrofurantoin and oral fosfomycin are generally not appropriate choices for cUTI because they may not achieve adequate levels in renal parenchyma and blood.

Figure 1.1: Four-step approach to choosing empiric antimicrobial therapy for cUTI



This approach starts with the most important issue—the patient's severity of illness—and then takes into consideration the patient's risk factors for having a pathogen resistant to specific antibiotics or antibiotic classes, as well as practical issues such as antibiotic allergies. Finally, and only for patients with sepsis related to cUTI, the local antibiogram may have a role in helping the provider avoid inappropriate empiric antibiotic therapy if it is recent and relevant to the patient under consideration. The antibiogram is the last of the four recommended steps, as the evidence that using a facility's antibiogram to guide antibiotic prescribing for individual patients improves outcomes is very uncertain. Choosing which organism to focus on in the antibiogram is also a challenge in empiric decision making. The most relevant organism is suggested by the prior urine culture, if available. If not, *E. coli* is the default organism.

Introduction

Complicated UTI (cUTI) is one of the more common reasons for emergency department visits and hospital admission. Selection of appropriate empiric antibiotics for cUTI can be complex because of increasing resistance to antibiotics used to treat UTI, the association between active empiric therapy and improved outcomes in UTI, and the availability of newer and broader spectrum agents. Many new antibiotics have received FDA approval for treating cUTI since the prior IDSA UTI guidelines on cystitis and pyelonephritis were published. The randomized, controlled trials to gain these FDA approvals provide a rich evidence base about the efficacy of various antibiotics for empiric treatment of cUTI. As these trials followed FDA

guidance about cUTI trial design, most are similar in design (non-inferiority) and patient populations. This is, at once, both a strength and a weakness of the evidence base. For example, we can draw comparisons across trials (assuming similar prevalence of resistance), but the inclusion/exclusion criteria were selected for a younger population with few comorbidities and often excluded patients in septic shock. Mortality in the trials that accepted patients without specifying a resistant uropathogen as an inclusion criterion was accordingly low (< 1% in all), which may not reflect real-world survival for patients hospitalized with cUTI. Another common design feature in these randomized, controlled trials is that clinical and microbiological outcomes were assessed at "test of cure," usually 5-10 days after completion of antibiotics. In clinical practice, patients who are feeling better after treatment for cUTI or acute pyelonephritis do not typically return for clinical assessment or repeat urine cultures. In fact, collection of a urine culture in a now asymptomatic patient is discouraged in clinical practice guidelines as asymptomatic bacteriuria (ASB) treatment does not prevent UTI and may predispose to subsequent recurrent UTI.[1-4] Uncertainty over the clinical relevance of ASB at the test of cure study visit influenced the panel's choice of important outcomes, as discussed below.

The scope of this clinical question was limited to empiric choice of antibiotics in suspected cUTI. If the causative organism has already been identified as a difficult-to-treat resistant pathogen, please refer to the IDSA guidance on antimicrobial resistance.[5] For patients with septic shock from a urinary source, in addition to using these cUTI guidelines to guide empiric antimicrobial therapy, please refer to the Sepsis-3 Task Force guidelines for other management strategies.[6] The guidelines below first discuss the evidence for specific antibiotics or classes of antibiotics that can be used as empiric therapy for cUTI. Then, the stepwise approach is discussed, with explanations of the evidence on the potential impact of inappropriate initial antibiotic therapy, the predictive value of specific risk factors for having a resistant uropathogen (including prior urine cultures and prior antibiotic exposure), and modeling approaches for establishing what threshold to use on the antibiogram when choosing empiric antibiotics for a cUTI patient with sepsis.

Background on the trials providing evidence about specific antibiotics for cUTI

All but five of these 15 published trials discussed here were designed as FDA registration trials to gain an FDA indication for a novel agent's use in cUTI and pyelonephritis (See **Table A.1** "Characteristics of Included Studies" in the Supplementary Materials). Thus, most trials followed the FDA-recommended non-inferiority design and largely demonstrated that the newer agents are non-inferior to older antibiotics. Patients enrolled in these randomized, controlled trials may not reflect the real-world population with cUTI; many of the randomized, controlled trials had a low mortality rate (1% or less) compared to the above 5% mortality rates reported in observational studies examining the consequences of inappropriate empiric antimicrobial therapy (IEAT) in cUTI. Another important caveat is that clinical and microbiological outcomes in some trials were affected by high levels of uropathogen resistance to one of the antibiotics under comparison (such as fluoroquinolones or ceftriaxone).

The aim of our systematic review was to assess the balance of benefits and harms for currently used antibiotics (especially in the context of increasing resistance) as well as the drugs newly available in the US since 2008. We found antimicrobial agents were generally comparable in terms of achieving clinical cure as long as the causative pathogen was susceptible to the agent given, and we conclude that other factors, such as patient risk factors for resistance to specific antibiotics, antibiotic stewardship considerations, drug adverse event

profiles, and cost should drive choice among these agents. A decisional strategy for selecting empiric therapy in cUTI will be presented.

Methods for reviewing specific antibiotic classes for empiric treatment of cUTI

To understand the evidence presented, it is important to appreciate the following issues: the choice of antibiotics, the timeframe of the studies, the background level of antibiotic resistance, the prioritization of outcomes, and the clinical decision threshold. The panel's decisions on the choice of antibiotics and years of publication are addressed below. Please see the introduction for a discussion of the prioritization of outcomes and selection of a clinical decision threshold. The background level of antibiotic resistance is addressed under each specific class of antibiotics, in the context of the studies that provided the supporting evidence.

Choice of antibiotics:

The panel established some criteria for which antibiotics to include in these cUTI guidelines. The antibiotic needed to be available in the United States, which implies FDA approval (although not necessarily for a UTI indication). Drugs that sought but did not attain FDA approval for cUTI were not included in our evidence tables, but we discuss several of these drugs below.

Years of publication:

The literature search for randomized, controlled trials of empiric treatment of cUTI started in 2008, updating from prior guidelines. To gather evidence on risk factors for having an organism resistant to specific antibiotics or for more general concepts related to cUTI treatment, literature searches started in 2000. Some older antibiotics have not been tested in a randomized, controlled trial since 2008 but may still have relevance to empiric treatment of cUTI; for such antibiotics, we looked at literature reviews and provided narrative discussion. Ampicillin-sulbactam, cefazolin, and trimethoprim-sulfamethoxazole (TMP-SMX) have not been tested in an RCT for cUTI since 2008; their ongoing relevance to empiric treatment of cUTI is unclear due to the high prevalence of resistance among *Escherichia coli* to these antibiotics. Many antibiotics included in our search strategy were not actually studied in any of the references identified to form the evidence base for this clinical question (e.g. many cephalosporins), and recommendations could be made only via indirect evidence from similar/nearly equivalent antibiotics.

Our literature searches for clinical trials of various antibiotics to treat cUTI extended back to studies published in 2008, picking up where the prior UTI guidelines' literature review stopped. Although the prior UTI guidelines focused on cystitis and pyelonephritis in premenopausal women, the panel judged that literature prior to 2008 would not be relevant to management of cUTI in the current era. In particular, the prevalence of antibiotic resistance among urinary pathogens has changed considerably from 2008 to the present (2023). Additionally, many prior first-line antibiotics for cUTI (e.g., aminoglycosides and ceftriaxone) were rarely studied in randomized, controlled trials from 2008-2023, as much older trials had established their efficacy. The clinical trials gathered to address this clinical question, along with important contextual information such as the main uropathogens isolated and their rates of resistance to the study antibiotics, are given in the Supplemental Materials (Table "Characteristics of the Included Studies").

Antibiotics' effectiveness in these trials related to the prevalence of resistance among uropathogens to each of the two study drugs in the study population at the time. Usually, the

comparator in a given trial was an older agent with a higher prevalence of resistance among the isolated uropathogens. An unconfounded comparison would require the prevalence of resistance to each study drug to be the same. In these guidelines' supporting text and tables, we have reported resistance rates in two different ways: (1) general rate of resistance to a specific antibiotic among all bacteria isolated, tested, and reported in that trial, or (2) the specific rate of resistance to an antibiotic within a treatment group (i.e. the people actually receiving that drug).

Summary of Evidence for Specific Antibiotic Classes for Empiric Treatment of cUTI

Different classes of antibiotics that can be used as empiric therapy for cUTI will be discussed below. Doses of the antibiotics used in these studies are in **Table 2.1** below.

Table 2.1: Dosing of intravenous (IV) antibiotics for complicated UTI used in clinical studies presented in alphabetical order.

Drug	Dosing regimen used in clinical trials for patients with normal renal function
Cefepime	1-2g every 8 to 12 hours[7,8]
Cefepime-enmetazobactam	2g/0.5g (infused over 2 hours) every 8 hours[9]
Cefiderocol	2g (infused over 3 hours) every 8 hours[10,11]
Cefotaxime	1-2g every 8 hours[12]
Ceftazidime	1-2g every 8 hours[13,14]
Ceftazidime-avibactam	2.5g (infused over 2 hours) every 8 hours[15-17]
Ceftolozane-tazobactam	1.5g every 8 hours[18]
Ceftriaxone	1-2g daily[19,20]
Ertapenem	1g daily[20]
Fosfomycin	6g every 8 hours[21]
Imipenem-cilastatin	500mg every 6 hours[17,22] 1g every 8 hours[11]
Imipenem-cilastatin-relebactam	500mg/125mg every 6 hours[22]
Meropenem	1g every 8 hours[19,23]
Meropenem-vaborbactam	2g/2g (infused over 3 hours) every 8 hours[24]
Piperacillin-tazobactam	4.5g every 8 hours[9,21,24]
Plazomicin	10-15mg/kg daily[23,25]

Table 2.1 includes IV dosing for cUTI based on review of randomized controlled trials among patients with complicated UTI.

1) Ceftriaxone / third and fourth generation cephalosporins

Ceftriaxone (and to a lesser extent, other parenteral third and fourth-generation cephalosporins) have a long history of use to treat cUTI including pyelonephritis, including a recommendation in the prior IDSA UTI guidelines of these agents as appropriate treatment for women with acute pyelonephritis.[26] While the increasing prevalence of Enterobacterales producing extended-spectrum beta lactamases threatens to undermine the efficacy of

ceftriaxone and other antibiotics in its class, ceftriaxone remains a frequent choice for empiric therapy of cUTI.

Summary of evidence for empiric use of ceftriaxone to treat cUTI

The key studies establishing the efficacy of ceftriaxone for treatment of cUTI were published prior to our literature search's time frame of 2008-2023. Two randomized, controlled trials compared ceftriaxone and the newer agent ertapenem for cUTI (including acute pyelonephritis), and the findings were summarized in a meta-analysis.[27-29] In both studies patients received the antibiotic IV initially, and then a switch to oral agents was permitted after three days of treatment, to complete 10-14 days total therapy. The most commonly used oral agent was a fluoroquinolone. Of the 850 randomized patients in the combined trials, 480 cases were microbiologically evaluable. The primary efficacy endpoint in these trials was not clinical cure but microbiologic cure at the test of cure visits, 5-9 days after completion of therapy. The primary outcome (microbiologic response) was achieved in 91% in the ceftriaxone arm versus 90% of patients in the ertapenem arm (risk difference (RD): 0.9%; 95% CI, -4.5% to 6.3%). Clinical response was not reported. Baseline resistance to ertapenem and ceftriaxone was not observed in these trials except for a few enterococci and *P. aeruginosa* isolates.[28]

Only one RCT was identified in our present literature search, which reported the results of a multi-center trial from South Korea comparing ceftriaxone to ertapenem for empiric treatment of cUTI (Park 2012).[20] After five days of IV therapy, patients could be switched to oral ciprofloxacin or cefixime to complete 10-14 days of antibiotic therapy. Among the 267 patients enrolled from 2008-2009, uropathogen resistance to ceftriaxone was only 6.2% (including 4.5% ESBL-producing organisms).

Benefits, Harms and Certainty of evidence

The single trial identified in our present literature review reported only a combined endpoint of clinical cure and microbiological response, both assessed at 5-9 days after completion of antibiotic therapy (i.e. data on clinical cure alone were not available).[20] Treatment with ceftriaxone may lead to similar cure rates (cure being a composite of clinical and microbiologic outcomes) in comparison to ertapenem, but the evidence is very uncertain mainly due to serious imprecision (i.e. small sample size). Specifically, the overall combined clinical cure and microbiological response reported in this single trial was 87% for ceftriaxone vs 88% for ertapenem (RD: -0.6%; 95% CI: -11.6% to 10.5% / relative risk (RR): 0.99; 95% CI: 0.88 to 1.13; very low certainty of evidence). For microbiologic cure, ceftriaxone may lead to similar rates of microbiological cure as ertapenem (RD: 0.9%; 95% CI: -9.9% to 11.6% / RR: 1.01; 95%CI: 0.89 to 1.14). Recurrence of infection was not reported in this study.
Patients treated with ceftriaxone may experience fewer non-serious adverse events than the comparator group (4.4% in ceftriaxone group vs 10.6% in ertapenem group), with the ceftriaxone group experiencing fewer drug-related gastrointestinal adverse events (diarrhea and nausea). No serious adverse events were documented, and mortality was not reported.

Other considerations

Ceftriaxone is a practical choice for outpatient antibiotic therapy programs when the once-daily dose is sufficient, both for ease of dosing and for its low cost relative to newer agents. It can also be administered intramuscularly, which can be a particularly useful route in

patients who lack sensation in lower limbs or gluteal areas due to spinal cord injury. Ceftriaxone susceptibility cannot be extrapolated to cefpodoxime or cefepime.

The 2010 publication of the UTI guidelines on cystitis and pyelonephritis recommended a single dose of aminoglycoside or ceftriaxone at the initiation of oral antibiotics to treat acute pyelonephritis, if resistance to the oral agent was a concern.[26] We identified one study of single dose ceftriaxone in non-pregnant adults; this study suggested that a single dose of IV ceftriaxone prior to switching to an oral cephalosporin was an effective strategy for women with pyelonephritis.[30]

Rationale for recommendation and implementation

The panel judged that ceftriaxone, and by extension third and fourth generation cephalosporins remain one of the preferred classes of antibiotics to empirically treat patients with cUTI, particularly in patients without sepsis. If after applying the four empiric antibiotic choice steps (severity of illness, risk factors for resistance, patient-specific factors, and antibiogram), third or fourth generation cephalosporins have not been excluded from consideration, they may be appropriate empiric choices for patients with sepsis related to cUTI.

As an example of applying the four steps, if the patient had an ESBL-producing organism in a recent prior urine culture, ceftriaxone would not be an appropriate choice for cUTI. As another example, if the prevalence of ceftriaxone resistance exceeds 10% or 20%, ceftriaxone should not be used as empiric therapy for patients with cUTI in septic shock or sepsis, respectively.

2) Piperacillin-tazobactam

Piperacillin-tazobactam is an extended-spectrum penicillin and beta-lactamase inhibitor combination with broad activity against Gram-negative organisms, including *Pseudomonas aeruginosa*. Since its approval in 1993, recommended doses of piperacillin-tazobactam have been increased to overcome rising MICs in common pathogens; for the same reason, many sites now employ extended or continuous infusion piperacillin-tazobactam dosing strategies.

Summary of evidence for the empiric use of piperacillin-tazobactam to treat cUTI

Three randomized, controlled, multicenter, international trials included piperacillin-tazobactam as a treatment group for cUTI, including 2,043 evaluable patients with cUTI or acute pyelonephritis (per the FDA definitions).[9,21,24] The aim of these FDA registration trials was to establish the efficacy of novel agents (cefepime-enmetazobactam, meropenem-vaborbactam and IV fosfomycin) versus piperacillin-tazobactam in cUTI/acute pyelonephritis. The TANGO I study (Kaye 2018) compared meropenem-vaborbactam (a novel beta-lactam, beta-lactamase inhibitor, or BLBLI) to piperacillin-tazobactam in 545 patients with cUTI.[24] Patients received an average of 8 days of IV therapy, followed by 2 more days of oral levofloxacin. The ZEUS study (Kaye 2019) compared IV fosfomycin to piperacillin-tazobactam in 464 patients, with 7 days of IV therapy and no oral switch options.[21] In these two trials, resistance to piperacillin-tazobactam was 7% and 13%, while resistance to meropenem was 1% and resistance to the two novel drugs (IV fosfomycin and meropenem-vaborbactam) was not reported. The ALLIUM study (Kaye 2022) compared cefepime-enmetazobactam (a novel BLBLI) to piperacillin-tazobactam in

1,034 with cUTI.[9] Patients also received an average of 8 days of IV therapy and no transition to oral antibiotic was allowed. Patients with resistant uropathogens to either studied drugs were excluded from the analysis. For all three studies, clinical and microbiological outcomes were assessed at test of cure, 7-14 days after end of antibiotics.

Benefits, Harms and Certainty of evidence

Treatment with piperacillin-tazobactam (PT) likely leads to the similar rate of clinical cure at the test of cure timepoint as does treatment with comparators in patients treated for cUTI (overall clinical cure for PT was 88.9% vs 91.5% for comparators; RD: -2.7%; 95% CI: -5.5% to 0.9%/ RR: 0.97; 95% CI: 0.94 to 1.01; moderate certainty of evidence).

The evidence suggests that piperacillin-tazobactam leads to lower microbiological cure at test of cure than the comparators. Overall, microbiological eradication for piperacillin-tazobactam was 60.8% versus 74.2% in the comparator group (RD: -14.1%; 95% CI: -17.8% to -9.6%/ RR: 0.81; 95% CI: 0.76 to 0.87). Recurrence of infection was recorded only in one trial (Kaye 2019) at late follow up. The evidence suggests that treatment with piperacillin-tazobactam leads to similar recurrence of infection rates, as compared to IV fosfomycin (3.9% with piperacillin-tazobactam versus 4.3% with fosfomycin), but this estimate is likely imprecise due to the few events.

The evidence suggests that serious adverse events and mortality were comparable between the two groups (mortality rate was 0.5%). Non-serious adverse events were lower in patients receiving piperacillin-tazobactam versus the comparators (RD: -6.6%; 95% CI: -10.4% to -2.4%/ RR: 0.86; 95% CI: 0.78 to 0.95).

Other considerations

Administration of piperacillin-tazobactam requires an increasingly thoughtful approach, with improved time above the MIC for many pathogens more likely to be achieved through prolonged or continuous infusion. Such dosing strategies create challenges for nursing staff, pharmacists, and patients. Piperacillin-tazobactam is formulated as a salt and can cause hypokalemia or fluid overload. Rising rates of ESBL-producing organisms and multidrug-resistant *Pseudomonas* are challenging the effectiveness of piperacillin-tazobactam.

Rationale for recommendation and implementation

The panel judged that piperacillin-tazobactam remains one of the preferred antibiotics for empiric treatment of patients with cUTI without sepsis. If after applying the four empiric antibiotic choice steps (severity of illness, risk factors for resistance, patient-specific factors, and antibiogram), piperacillin-tazobactam has not been excluded from consideration, it may be an appropriate empiric choice for patients with sepsis related to cUTI.

As an example of applying the four steps, if the patient had an organism resistant to piperacillin-tazobactam in a recent prior urine culture, piperacillin-tazobactam would not be an appropriate choice for cUTI. As another example, if the prevalence of piperacillin-tazobactam resistance exceeds 10% or 20%, piperacillin-tazobactam should not be used as empiric therapy for patients with cUTI in septic shock or sepsis, respectively.

3) Fluoroquinolones

The fluoroquinolones (FQ) have a long history in treatment of urinary tract infections, including pyelonephritis, with the first clinical trials of quinolones to treat UTI appearing nearly 40 years ago.[31,32] While fluoroquinolones are very useful for treating infections of the urinary tract and have excellent oral bioavailability, they also have an important role in treating respiratory infections, bone and joint infections, enteric pathogens, *Pseudomonas aeruginosa*, mycobacteria, and *Neisseria spp*. Unfortunately, widespread use and overuse of fluoroquinolones have led to both dramatic increases in bacterial resistance and a better appreciation of these agents' potential for serious side effects, including collagen-vascular adverse events (tendinitis, tendon, and aortic aneurysm or dissection rupture), peripheral neuropathy, central nervous system effects, hypoglycemia, QT interval prolongation, and *C. difficile* colitis. In 2016 the FDA issued advice that in light of the potentially severe side of effects of fluoroquinolones, these drugs should not be used to treat uncomplicated UTIs in patients who have other treatment options.[33] Given the rising resistance, concern for serious toxicities, and important role quinolones play in more serious infections, many antibiotic stewardship programs have focused on reducing fluoroquinolone use in cUTI.

Summary of evidence for empiric use of fluoroquinolones to treat cUTI

Our literature search from 2008-2023 identified three randomized, controlled trials of empiric treatment of cUTI using a fluoroquinolone (levofloxacin).[18,25,34] These were multicenter, international trials conducted to establish the efficacy of new drugs to treat cUTI (including acute pyelonephritis) and gain FDA approval for cUTI. A total of 1,956 patients were treated for complicated UTI/acute pyelonephritis (as defined by the FDA) in these studies, with enrollment spanning 2003-2013. The prevalence of fluoroquinolone resistance was increasing during this period, and levofloxacin resistance among uropathogens isolated in these trials ranged 15-27% compared to 0.5-6% for the novel comparator agents, which were doripenem (Naber 2009),[34] ceftolozane-tazobactam (ASPECT-cUTI trial, Wagenlehner 2015),[18] and plazomicin (Connolly 2018).[25,35] Patients received IV antibiotics for 5-7 days; one trial permitted additional oral therapy with levofloxacin (Naber 2009). Clinical and microbiologic outcomes were measured at the test of cure (TOC) visit, 5-12 days after the last dose of antibiotics.

Benefits, harms, and certainty in the evidence

Despite the much higher resistance rates to fluoroquinolones than to the comparators, empirical treatment of suspected cUTI/acute pyelonephritis with fluoroquinolones (FQ) likely leads to lower clinical cure rates at test of cure versus the comparators, but this difference was judged clinically unimportant at a decision threshold of 10% (see Methods section on decision threshold). More specifically, clinical cure for FQ was 88.2% vs 91.3% for the comparator group (RD: -3.7%; 95% CI: -6.4% to -0.9%; RR:0.96; 95% CI: 0.93 to 0.99/ moderate certainty of evidence).

Interestingly, fluoroquinolones may lead to similar rates of microbiological cure as the comparators, but the evidence is very uncertain. Microbiological cure in the FQ was 75.9% and was 79.2% in the comparator group (RD: -3.2%; 95% CI: -11.1% to 4.8%/ RR: 0.96; 95% CI: 0.86 to 1.06).

The lower rates of clinical cure with fluoroquinolones are likely explained by the much higher resistance rates to fluoroquinolones versus the new drugs among the isolated uropathogens. One trial performed a post-hoc analysis to analyse the subgroup of patients found to have a fluoroquinolone-resistant pathogen in the ASPECT-cUTI trial (ceftolozane-

tazobactam).[35] A total of 212 patients mainly with acute pyelonephritis and levofloxacin-resistant uropathogens were analysed. In these patients whose baseline organism was resistant to levofloxacin, empirical treatment with levofloxacin was associated with lower rate of clinical cure at TOC (RD: -13.2%; 95% CI: -23.0% to -3.4%). Interestingly, overall response rates in these patients with levofloxacin-resistant uropathogens (i.e. regardless of antibiotic treatment) were lower than in the parent study (83% vs 90% respectively) which suggests that these patients' infections might be more difficult to cure either due to differences in the uropathogens, differences in the patients' risk factors for having UTI, or both. These findings are congruent with multiple observational studies suggesting that patients infected with resistant organisms more often have comorbidities or risk factors for poor outcomes than patients with more susceptible organisms.[36-39]

Recurrence of infection at late follow up was reported only in one study.[18] This evidence suggests that treatment with fluoroquinolones may lead to similar rates of recurrence of infection as the comparators (6% with levofloxacin versus 14% with ceftolozane-tazobactam; RD: -8%; 95% -13.6% to 37.0%),[18] but this estimate is likely imprecise due to the few events and a very small sample size. Serious and non-serious adverse event rates were likely comparable between groups. Mortality was rare (0.1%).

Other considerations

Other considerations specific to fluoroquinolones include their ease of administration, low cost, potential for serious adverse events, and antibiotic stewardship concerns. Fluoroquinolones have excellent bioavailability, with the IV to oral switch being dictated by when the patient can take oral drugs rather than concerns about bioavailability. Antibiotic stewardship concerns are perhaps more relevant to this class of antibiotics than others given that two recent antimicrobial resistance surveillance reports found that approximately 30% of Enterobacterales isolates were resistant to fluoroquinolones in a national study of hospitalized patients,[40] while the SENTRY report on bloodstream isolates 2012-2017 found that 30% of *E. coli* were resistant to ciprofloxacin.[41]

Rationale for recommendation and implementation

The panel judged that fluoroquinolones remain one of the preferred classes of antibiotics to empirically treat patients with cUTI without sepsis, despite the possibility of lower clinical cure rates in patients with fluoroquinolone-resistant uropathogens, because cUTI-related mortality is low in the absence of sepsis. If, after applying the four empiric antibiotic choice steps (severity of illness, risk factors for resistance, practical considerations, and antibiogram), fluoroquinolones have not been excluded from consideration, they may be an appropriate empiric choice for patients with sepsis related to cUTI. Fluoroquinolones as a class can be very effective therapy for cUTI but should be reserved for cases in which resistance is not expected.

As an example of applying the four steps, if the patient had taken a fluoroquinolone within the past 12 months or had a recent urine culture with a fluoroquinolone-resistant organism, a fluoroquinolone would not be an appropriate choice for cUTI. As another example, if the prevalence of fluoroquinolone resistance exceeds 10% or 20%, fluoroquinolones should not be used as empiric therapy for patients with cUTI in septic shock or sepsis, respectively. Caution is advised in applying these recommendations because the studies with supporting evidence last enrolled patients in 2013, and the rate of resistance to fluoroquinolones has increased since that time.

4) Carbapenems (without beta-lactamase inhibitors or BLI)

Carbapenems have a broad spectrum of activity and stability against many beta-lactamases, though carbapenem-resistant organisms are an increasing concern.[42-44] Given carbapenems' value as empiric therapy for suspected Gram-negative bacterial infections in the critically ill, preserving carbapenem effectiveness is a high priority for antibiotic stewardship programs. In this section, we discuss clinical trials of imipenem-cilastatin, ertapenem, meropenem, and doripenem for complicated urinary tract infections (cUTIs). None of these drugs have an oral option. Discussion of tebipenem and sulopenem (neither approved in the US at the time this passage was written) appears elsewhere.

Summary of the evidence for empiric use of carbapenems (without BLI) to treat cUTI

We identified seven randomized, controlled trials published from 2009-2019 (total n=3554 patients) that compared a carbapenem to alternative therapy for cUTI and/or acute pyelonephritis.[11,15-17,20,23,34] In two of the older trials, carbapenems were the new drug of interest, compared to fluoroquinolones (Naber 2009)[34] or ceftriaxone (Park 2012).[20] In five of the trials, carbapenems were the older comparator, and the drug of interest was a novel beta-lactam, beta-lactamase inhibitor combination (Vasquez 2012, Wagenlehner 2016, Carmeli 2016),[15-17] plazomicin (Wagenlehner 2019),[23] or cefiderocol (Portsmouth 2018).[11]

Antimicrobial susceptibilities of the uropathogens in these trials are key context for interpreting their results. For example, resistance to ceftriaxone in the Park 2012 study was 6.2%,[20] and resistance to levofloxacin was 14.8% in the Naber 2009 study;[34] in contrast, resistance to carbapenems in both studies was less than 1%. These high resistance rates to the older comparator would favor carbapenems. On the other hand, in the studies published from 2016 onwards, resistance rates to carbapenems ranged from 3-5%, while resistance to the novel agents was rare.[11,15,16] The average duration of IV therapy in these trials ranged from 5-10 days, and some studies continued with oral therapy based on the susceptibility of the isolated organisms.

Benefits, harms, and certainty of evidence

Treatment with carbapenems likely leads to similar rates of clinical cure as the antibiotic comparators at test of cure across these seven studies. Specifically, clinical cure in patients with cUTI treated with carbapenems was 91.2% vs 89.9% for comparators (RD: 1.8%; 95% CI: -0.9% to 3.6%/ RR: 1.02; 95% CI: 0.99 to 1.04; moderate certainty of evidence). The test of cure visit was typically 7-10 days after the last dose of antibiotics.

The evidence suggests that treatment with carbapenems leads to fewer microbiological cure (at TOC) versus the comparators, but this reduction was judged clinically unimportant at a decision threshold of 10%. More specifically, the microbiologic cure was 72.8% in patients treated with carbapenems than 80.4% with comparators (RD: -8.8%; 95% CI: -13.7% to -2.4%/ RR: 0.89; 95% CI: 0.83 to 0.97), but three of the seven trials accounted for the difference, each comparing carbapenems to a newer agent. Heterogeneity in this estimate is due to the EPIC trial,[23] in which the comparison was between meropenem and plazomicin, and the TOC visit was somewhat later than other trials, at 15-19 days after start of therapy. Another trial driving the microbiologic cure results against carbapenems was REPRISE, in which the comparison was between ceftazidime/avibactam and best available therapy (96% of which was a

carbapenem).[15] Only patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* were included in REPRISE. The third trial compared cefiderocol to imipenem-cilastatin, finding higher microbiologic cure at the TOC in the cefiderocol group than the imipenem group (73% versus 56%).[11] If these three trials are excluded, carbapenems might not have resulted in fewer microbiologic cures than the comparator antibiotics.

Only two of these seven trials reported the outcome of recurrent clinical infection, one of which was the EPIC trial of plazomicin,[23] and the other of which studied cefiderocol as the comparator.[11] In both trials clinical recurrence was measured 3-4 weeks after initiation of IV therapy. The evidence suggests that treatment with carbapenems leads to more recurrence of infection than the comparators in these two trials (8.2% vs 3.4%, respectively; RD: 6.1%; 95% CI: 1.6% to 14.8%/ RR: 2.80; 95% CI: 1.46 to 5.38). Of note, both trials also found a lower microbiologic cure rate in the carbapenem group, potentially implying a connection between microbiologic failure and recurrence of infection; again, however, whether this is a causative relationship (i.e. failing to kill the bacteria in the bladder leads to recurrence) or a linked relationship along a causal pathway (i.e. persistent bacteriuria is a marker for host factors such as urinary retention that also increase the risk of recurrent UTI) is unclear.

Mortality was rare in these randomized, controlled trials (0.4%), as expected given that life-threatening illness, expected imminent death, and serious comorbidities were frequent exclusion criteria. The rates of serious and non-serious adverse events were likely comparable between groups.

Other considerations

Other considerations specific to carbapenems include their crucial role in treating severely ill patients with healthcare-associated infections or risk factors for resistant pathogens. Carbapenems as a class are an important priority of antibiotic stewardship, to preserve their effectiveness.

Rationale for recommendation and implementation

The panel's overall assessment of the evidence was that carbapenems provide adequate clinical cure of cUTI in all studied comparisons. Carbapenems may be inferior to some newer agents (plazomicin, ceftazidime-avibactam, and cefiderocol) for microbiologic cure and prevention of recurrent infection, though the clinical relevance of the discrepancy between clinical and microbiologic cure is unclear.

Carbapenems clearly have a role in empiric treatment of cUTI in patients with sepsis and a higher risk of mortality. In the context of increasing rate of resistance to fluoroquinolones, third and fourth generation cephalosporins, and piperacillin/tazobactam, the panel considered carbapenems to be among the preferred antibiotics to empirically treat patients with sepsis assumed to be caused by cUTI, to avoid inappropriate empiric antibiotic therapy and possible associated excess mortality. However, in patients with cUTI without sepsis, the panel judged that carbapenems are not a first-line empiric antibiotic choice due to stewardship considerations, as initial drug-bug mismatch (causative organism not susceptible to the antibiotic given) in cUTI without sepsis is unlikely to substantially contribute to mortality, and clinical cure is still achieved in the majority of cases.

5) Novel beta-lactam/beta-lactamase inhibitors (BLBLI)

Multidrug-resistant and difficult to treat Gram-negative uropathogens such as carbapenem-resistant Enterobacterales (CRE) uropathogens such as Klebsiella-pneumoniae carbapenemase-producing (KPC) *E. coli,* multidrug resistant *Pseudomonas aeruginosa*, *Acinetobacter spp.*, and *Stenotrophomonas maltophilia* have increased the challenge of treating cUTIs.[45] To meet this challenge, a welcome number of new drugs have been developed, including novel beta-lactams and beta-lactamase inhibitor combinations (BLBLIs). In recent years, ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam, and cefepime-enmetazobactam have all been approved for use in treating cUTI following one or more FDA registrational trials. In most of these agents the novel beta-lactamase component has been designed to inhibit the activity of beta-lactamases, including certain carbapenemases. In parallel with development of these new combination antibiotics, molecular tests to define the specific resistance genes expressed by the bacterial pathogen are also coming into widespread use. Antibiotic stewardship considerations suggest that the main role of novel BLBLIs currently may be in treating identified multidrug-resistant pathogens, particularly when the resistance gene or mechanism has been established.

Summary of evidence for empiric use of novel beta-lactam/beta-lactamase inhibitors to treat cUTI

The evidence for the use of novel BLBLI in treatment of cUTI include seven randomized, controlled trials, published from 2012-2023 and including 4,432 patients with cUTI (including acute pyelonephritis). All trials evaluated the efficacy of a novel BLBLI versus a standard cUTI comparator, including levofloxacin in the ASPECT-cUTI (Wagenlehner 2015) trial,[18] carbapenems in four trials (Vasquez 2012, Wagenlehner 2016, Carmeli 2016, Sims 2017),[15-17,22] and piperacillin-tazobactam in the TANGO I and ALLIUM trials (Kaye 2018 and Kaye 2022).[9,24] The average duration of IV therapy ranged from 5-10 days, and some trials transitioned patients to oral therapy with a fluoroquinolone or TMP/SMX. Clinical cure and microbiologic cure were usually measured at TOC, 5 to 10 days after end of antibiotic therapy.

Benefits, Harms and Certainty of evidence

Overall, treatment with the novel BLBLIs likely leads to similar clinical cure as the comparator antibiotics at test of cure in patients with cUTI (overall clinical cure for novel BLBLIs was 91.9% vs 89.7% for comparators; RD: 0.9%; 95% CI: -0.9% to 3.6%/ RR: 1.01; 95% CI: 0.99 to 1.04; moderate certainty of evidence).

The evidence suggests that treatment with novel BLBLIs leads to more microbiological cures at test of cure in patients with cUTI versus comparator antibiotics, but this increase was judged clinically unimportant at a decision threshold of 10% (. More specifically, microbiological cure for novel BLBLI was 79.3% and 69.0% for the comparators (RD: 8.3%; 95% CI: 1.4% to 15.9%/ RR: 1.12; 95% CI: 1.02 to 1.23). When stratifying by classes of antibiotics in the comparator group, the difference in microbiological cure was larger when the comparator was piperacillin-tazobactam (RD: 15.0%; 95% CI: 8.1% to 22.4%). Microbiologic cure was more comparable with fluoroquinolones or carbapenems versus BLBLIs. Unfortunately, infection recurrence was not reported in these trials, so the relevance of in the higher microbiological cure rates with novel BLBLIs is unclear.

For harms, serious and non-serious adverse events were likely comparable between groups. Mortality was rare (0.4%), for reasons discussed above related to enrollment criteria for randomized, clinical trials.

Other considerations

Other considerations specific to these novel BLBLI agents are their crucial role in our current armamentarium against multidrug-resistant pathogens, and their higher costs as newer agents. The current role of these antibiotics in management of cUTI may be for use after identification of specific patterns of multidrug resistance. For example, IDSA guidance on antibiotic treatment of antimicrobial resistant Gram-negative infections suggests that the novel BLBLI agents be reserved for treating infections caused by organisms exhibiting carbapenem resistance.[5] Cost also becomes an important consideration with these agents. For example, according to the 2023 Wholesale Acquisition Cost (WAC) database, a dose of piperacillin/tazobactam ranges in cost from $30-$156, and meropenem costs $30-150 per dose, while ceftolozane/tazobactam costs $1443 per dose.[46] Higher costs can lead to inequities in access to these drugs, particularly if hospitals with underserved populations do not include these drugs on their formularies.

Rationale for recommendation and implementation

The novel BLBLIs have been designed to function against specific types of antibiotic resistance, particularly carbapenemases. From an antibiotic stewardship perspective, these drugs are among the few remaining options against multidrug resistant pathogens. As such, they should be reserved for situations in which they are truly needed, such as when susceptibility testing and molecular resistance testing results are available to guide the choice of novel BLBLI. When choosing empirically (prior to culture results) to treat a patient with cUTI, the panel judged that BLBLI are not first choice antibiotics because of these antibiotic stewardship considerations. Empiric use of novel BLBLIs for cUTI should be largely restricted to patients in septic shock for whom prior culture data or risk factors suggest that preferred antimicrobials are likely to be inappropriate.

6) Cefiderocol

Cefiderocol is a novel siderophore cephalosporin brought to the periplasm by bacterial iron transporters through a “Trojan horse” strategy, a unique mechanism of delivery conferring activity against many otherwise highly resistant Gram-negative bacteria.[45,47] Cefiderocol was approved by the FDA in 2019 for treatment of complicated UTI caused by susceptible Gram-negative microorganisms in patients who have limited or no alternative treatment options.[48] Unfortunately, resistance to cefiderocol, related to changes in siderophore receptors or traditional resistance mechanisms to cephalosporins, is already emerging.

Summary of evidence on empiric use of cefiderocol to treat cUTI

Two randomized, controlled trials were included, one of which focused specifically on cUTI caused by Gram-negative pathogens (Portsmouth 2018),[11] and the other which enrolled patients with serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR trial) (Bassetti 2021).[10] Both trials were multicenter and international. The Portsmouth trial enrolled 452 patients, all with cUTI, while CREDIBLE-CR enrolled 152 patients, of which only 36 had cUTI. The analyses below for clinical and microbiologic cure include 326

evaluable patients with cUTI. The comparator in the Portsmouth trial was imipenem-cilastatin, while the comparator in CREDIBLE-CR was best available therapy, of which the majority were colistin-based regimens. Although CREDIBLE-CR was randomized, the treatment was open label, and the duration of therapy was longer in the cefiderocol group (10.5 days versus 6.5 days).[10] Portsmouth 2018 was randomized and blinded, and duration of IV therapy averaged 9 days.[11] Test of cure in both studies was at 5-9 days after end of treatment.

Many of the causative organisms in these two multicenter, international trials were resistant to antibiotics. In the Portsmouth trial, despite excluding patients who were known to have an organism resistant to carbapenems, 6.5% of organisms were resistant to imipenem, 55% to levofloxacin, 28% to cefepime, and 15% to piperacillin-tazobactam.[11] The top three causative organisms were *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. In the CREDIBLE-CR trial, the organisms causing cUTI were predominantly *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and all organisms were resistant to carbapenems.[10] Surprisingly, 8/185 pathogens (4%) had a cefiderocol MIC of greater than or equal to 4 ug/mL at baseline in the main cohort.

Benefits, Harms and Certainty of evidence

Treatment with cefiderocol likely leads to similar clinical cure at test of cure in patients with cUTI versus the comparator antibiotics. . Specifically, clinical cure for cefiderocol was 88.5% vs 86.3% for comparators (RD: 2.6%; 95% CI: -4.3% to 10.4%/ RR: 1.03; 95% CI: 0.95 to 1.12; moderate certainty of evidence).

The evidence suggests that treatment with cefiderocol leads to higher rates of microbiological cures in at test of cure in patients with cUTI versus the comparator antibiotics. More specifically, microbiological cure at TOC for cefiderocol was 72.9% and 54.8% for the comparators (RD: 18.1%; 95% CI: 6.6% to 32.4% / RR: 1.33; 95% CI 1.12 to 1.59). The evidence suggests that cefiderocol leads to similar recurrence of infection at late follow-up (4.8% for cefiderocol vs 9.7% for the comparator group; RD: -4.8%; 95% CI -7.4% to 0.4% / RR: 0.50; 95% CI 0.24 to 1.04), but this estimate is imprecise due to the small number of recurrences documented.

Cefiderocol likely leads to fewer non-serious adverse events than the comparator antibiotics (RD: -11.1%, 95% CI: -18.7% to -2.5% / RR: 0.78; 95% CI: 0.63 to 0.95), but this finding was clearly driven by a high rate of gastrointestinal disturbances in the imipenem-cilastatin group in the Portsmouth 2018 trial. Serious adverse events were frequently reported in these studies. Cefiderocol may lead to comparable rates of serious adverse events (reported in 7.4% in the cefiderocol group and 10.8% in the comparator group) and mortality (1.5% in the cefiderocol group versus 1.3% in the comparator group) versus the comparators. The greater overall mortality with cefiderocol in CREDIBLE-CR appeared to be driven primarily by patients with hospital-acquired/ventilator-associated pneumonia or bloodstream infections and by infections with *Acinetobacter* spp..[10]

Other considerations

Other considerations specific to cefiderocol are that dosing needs to be adjusted carefully according to renal function, with increased frequency required to achieve therapeutic levels for patients on renal replacement therapy with augmented renal clearance (greater than 120 mL/min). As the Portsmouth 2018 trial excluded patients with creatinine clearance less than

20mL/min, the real-world impact of the need for dose adjustment on clinical outcomes remains to be seen.[11] Additionally, resistance to cefiderocol is already emerging. In the CREDIBLE-CR trial, 17% of enrolled patients in the cefiderocol arm received combination therapy, which may have boosted apparent effectiveness.[10] As a newer drug, the costs are expected to be higher than with older antibiotic agents.

Rationale for recommendation and implementation

The panel judged that cefiderocol is an alternative antibiotic to empirically treat patients with cUTI but is not preferred due to stewardship considerations and uncertainties about real-world effectiveness. Care should be taken to ensure adequate dosing in patients receiving renal replacement therapy. Cefiderocol's use may be ideally reserved for highly resistant uropathogens in which the resistance mechanism of the organism is known and should be overcome by cefiderocol (i.e. organisms with metallo-beta-lactamase carbapenemases).

7) Older aminoglycosides (gentamicin, amikacin, and tobramycin)

Aminoglycosides are among the earliest antibiotics to enter clinical use, though their use declined over the past half-century as alternative antibiotics with fewer side effects became available. As a class, aminoglycosides can cause renal impairment and ototoxicity, and these harmful effects often emerge during treatment despite optimized (i.e. once-daily) dosing. With rising rates of antimicrobial resistance, aminoglycosides are receiving renewed interest.

In this section we will discuss the indirect evidence for empiric use of older aminoglycosides (gentamicin, amikacin, and tobramycin) to treat cUTI. Plazomicin, the newest aminoglycoside, will be discussed separately.

No randomized, controlled trials of aminoglycoside monotherapy for empiric treatment of cUTI were published from 2008-2023; these agents were predominately tested in the last century. One systematic review of the literature and meta-analysis included 37 randomized, controlled trials published between 1966 up to 2006, mostly in adults.[49] These trials compared systemically administered aminoglycosides as a single drugs (monotherapy) versus another systemically administered single antibiotic or an antibiotic combination without aminoglycosides. The aminoglycosides studied were gentamicin, amikacin, tobramycin but also netilmicin (not currently available), and dosing was once daily in only three of these trials. The majority of the 26 UTI trials were published between 1981 and 1992 and included both inpatients and outpatients. Many of the UTI trials had very small sample sizes (34-186 patients), and only five reported on organisms' susceptibility to aminoglycosides. Comparator antibiotics were beta-lactam antibiotics (mostly cephalosporins) and quinolones.

Six of the UTI trials reported 30-day mortality, finding a statistically non-significant increase in mortality in the aminoglycoside arm (RR 1.96, 95% CI 0.61-6.29). Overall mortality in these studies were very low, precluding meaningful comparisons.

Twenty of the UTI trials reported on treatment failure, finding no significant difference between groups (RR 1.11, 95% CI 0.94-1.30). Microbiological failure at 5-9 days after end of therapy was higher in the aminoglycoside group in comparison to beta-lactams or quinolones (RR 1.40, 95% CI 1.16-1.69). During the timeframe of these trials, the cephalosporins and

quinolones were the newer drugs. Rates of relapse of infection were not significantly different between groups and were not reported further.

Adverse events were less often reported in the aminoglycoside group compared to the beta-lactams (RR 0.46, 95% CI 0.33-0.63), but the types of adverse events were different. Beta-lactams were associated with rash, phlebitis, gastrointestinal, and hepatic adverse events, while aminoglycosides were associated with nephrotoxicity, which was reported significantly more commonly in patients in the aminoglycoside group (RR 3.61, 95% CI 1.67, 7.80).

In summary, older trials (in which cephalosporins and quinolones were the novel agents without substantial resistance, and in which aminoglycoside resistance frequently went unreported) suggested similar performance of aminoglycosides versus comparators for cUTI, albeit with more nephrotoxicity. Many of these trials were too small to ensure randomization was successful and balanced for important characteristics, and these trials suffered from other methodologic flaws that limit their ability to inform modern clinical practice.

Summary of evidence for empiric use of older aminoglycosides to treat cUTI

More recently, two retrospective studies from Israel compared clinical outcomes of aminoglycosides to non-aminoglycoside antibiotics in patients hospitalized for cUTI between 2014-2019.[50,51] One study evaluated 2,026 patients with pyelonephritis (Elbaz 2020) of which 29% were bacteremic,[51] while the other studied 218 patients with bacteremia of urinary source with ESBL-producing Enterobacterales (Zohar 2019).[50] The rate of ESBL-producing organisms was 30% in the pyelonephritis study and 100% in the bacteremia study (by enrollment criteria). Patients in these two retrospective studies were older than patients in RCTs, with median ages of 79 and 82 years. The non-aminoglycoside antibiotics given were ceftriaxone, piperacillin-tazobactam, carbapenems, and fluoroquinolones. In both studies the primary outcome was 30-day mortality, and multivariate analysis was done to adjust for confounding variables. The mortality rate in the pyelonephritis study was 9.9% and16.6% in the bacteremia study, as expected with real-world data.

Benefits, harms and certainty of evidence

Both retrospective studies found that 30-day mortality was lower in the aminoglycoside group (ranging from RD: -2.4%, 95%CI: -3.9% to -0.6% / adjusted RR: 0.78; 95%CI: 0.65 to 0.95 to RD: -10.3; 95% CI: -21.4% to 0.8% / adjusted OR: 0.51; 95%CI: 0.24 to 1.06, but the certainty in the evidence is very low. Clinical cure was not reported, and microbiological cure was reported only in only one study. The evidence suggests that microbiological cure was comparable between groups (RD; -8.9%; 95%CI: -29.4% to 12.8% / adjusted OR: 0.70; 95%CI: 0.28 to 1.72), but this estimate was imprecise due to a very small sample size.[50]

Acute kidney injury may be comparable between groups in both studies (ranging from RD: -0.1%, 95%CI: -0.1% to 0% / adjusted RR: 0.98; 95%CI: 0.97 to 1.00 and RD: 1.3%; 95%CI: -5.4% to 14.4% / OR: 1.14, 95%CI (0.46 to 2.81) , but these estimates are very uncertain due to the serious risk of bias. Length of hospital stays and rehospitalization at 3 months may favor the aminoglycoside group in one study.[51]

Both studies found that patients who received aminoglycosides had fewer comorbidities, better renal function, and a better functional status than patients who received comparator

antibiotics. Confounding-by-indication with residual confounding remains very likely, despite authors' efforts to adjust for this selection bias. These clinical outcomes should be taken in the context that the patients treated with aminoglycosides were a relatively healthier group.

Other considerations

Aminoglycosides are now given once daily for cUTI,[52] and close consultation with a pharmacist is advised to adjust the dose and interval. Serious and irreversible nephro- and ototoxicity can occur with prolonged courses of therapy. Patients receiving these antibiotics require regular assessment of renal and otic function, and therapeutic drug monitoring to determine trough levels is recommended. Aminoglycosides may not be appropriate for patients with underlying impairment of renal function or hearing loss. Patients receiving IV or IM aminoglycosides as outpatients require close monitoring. These drugs are themselves inexpensive, although the laboratory tests add some costs.

The 2010 publication of the UTI guidelines on cystitis and pyelonephritis recommended a single dose of aminoglycoside or ceftriaxone at the initiation of oral antibiotics to treat acute pyelonephritis, if resistance to the oral agent was a concern.[26] This panel did not find any studies of single dose aminoglycoside as part of a combination treatment for cUTI in adults, but in practice one or two doses of an aminoglycoside are often used as a component of the antibiotic treatment for acute pyelonephritis/cUTI when there is a concern for an ESBL-producing organism.[53]

Rationale for recommendation and implementation

The panel judged that aminoglycosides are an alternative class of antibiotic for empiric treatment of patients with cUTI, especially in populations where the ESBL rate among urinary organisms is increasing. Many patients may have contraindications to receiving aminoglycosides, such as renal insufficiency or advanced hearing loss. The panel judged that aminoglycosides are not a preferred antibiotic for patients with cUTI with or without sepsis due to the relatively greater risk of nephrotoxicity and limited modern evidence base for effectiveness versus alternative agents.

8) Plazomicin

Plazomicin is a "next generation" intravenous aminoglycoside that was designed to evade bacterial aminoglycoside modifying enzymes.[45] These modifications give plazomicin activity against most Enterobacterales, including those resistant to older aminoglycosides. Plazomicin was approved by the FDA for use in complicated UTI in 2018. As with other aminoglycosides, plazomicin can cause nephrotoxicity; the risk of ototoxicity is less clear, but a valid safety concern that needs to be assessed in larger studies.

Summary of evidence for empiric use of plazomicin to treat cUTI

Two randomized, controlled, multicenter international trials compared plazomicin to another antibiotic in empiric treatment of cUTI, for a total of 744 evaluable patients.[23,25] One of these studies, Connolly et al. 2018 was a phase 2 study in which 145 patients were randomized to two different doses of plazomicin or levofloxacin IV for five days, and enrollment occurred between 2010-2012.[25] Resistance among the causative urinary pathogens was high, with 19% of all urinary pathogens resistant to levofloxacin, and 6% of pathogens resistant to plazomicin.

Oral switch at end of therapy was not permitted. Once the trial was underway, enrollment in the lower plazomicin treatment dose group (10mg/kg) was stopped, and all patients were subsequently randomized to the higher (15mg/kg) dose versus levofloxacin. In the EPIC trial (Wagenlehner 2019), 604 patients were randomized to receive IV plazomicin versus meropenem for an average of five days and then were transitioned to oral agents to complete 7-10 days of therapy.[23] The majority of organisms isolated were susceptible to both plazomicin and meropenem. The test of cure visit was at 15-19 days after starting IV therapy for the EPIC trial; the Connolly 2018 trial measured test of cure at 5-12 days after the end of antibiotic treatment. Patients in both trials had to have good renal function (creatinine clearance of >60 ml/min in Connolly and >30 mL/min in the EPIC trial).

Benefits, Harms and Certainty of evidence

Treatment with plazomicin likely leads to similar rates of clinical cure at TOC in patients with cUTI versus treatment with comparator antibiotics. Specifically, the overall clinical cure for plazomicin was 84.3% vs 87.2% for comparators (RD: 0.0%; 95% CI: -6.1% to 6.1%/ RR: 1.00; 95% CI: 0.93 to 1.07; moderate certainty of evidence).

Treatment with plazomicin may lead to higher rates of microbiological cure at test of cure in patients treated for cUTI versus the comparator antibiotics (plazomicin was 81.9% vs comparator group was 72.6%; RD: 12.3%; 95% CI: 5.1% to 21.0% / RR: 1.17; 95% CI: 1.07 to 1.29). The evidence suggests that treatment with plazomicin may lead to similar recurrence of infection at late follow-up (3.2% in the plazomicin group vs 7.0% in the comparator group), but these studies are too heterogeneous to be pooled since these they reported opposite direction of effects.

Although plazomicin likely leads to similar rates of non-serious adverse events versus comparators, but an increase in serum creatinine of 0.5 mg or more per deciliter above baseline was observed in 7.0% in the plazomicin group vs 4.0% in the meropenem group in the EPIC trial,[23] and ototoxicity was reported in two cases (one in each group). Connolly 2018 required enrolled patients to have a creatinine clearance of >60ml/min at baseline, and five plazomicin-treated patients had an increase in serum creatinine of >=0.5 mg/dl during the study, versus one levofloxacin-treated patient.[25] Two patients in the plazomicin group and one in the levofloxacin group developed some signs of ototoxicity. Serious adverse events and mortality were rare (only 1 death among 744 patients). In the context of the relative healthy state of the enrolled subjects compared to the real-world population of patients hospitalized with cUTI, these signals of nephro- and otoxicity are concerning.

Other considerations

Other considerations specific to plazomicin include the need to involve a clinical pharmacist in designing and monitoring the once daily dosing regimen, to avoid nephro- and ototoxicity. Patients with baseline renal impairment and hearing loss may not be good candidates to receive this agent. Patients with creatinine clearance of < 30 mL/min were excluded from the clinical trials of this agent. Plazomicin is generally a more expensive antibiotic than the older agents.

Rationale for recommendation and implementation

The panel judged that plazomicin is an alternative antibiotic to empirically treat patients with cUTI but is not preferred due to concerns with potential serious adverse events associated with aminoglycosides, such as renal insufficiency or ototoxicity.

9) Oral empiric antibiotics for cUTI

Some patients with cUTIs who are seen in an emergency department or urgent care setting with acute pyelonephritis may be candidates for outpatient management. Similarly, patients with CAUTI seen in clinic may often be managed as outpatients. Oral third generation cephalosporins and fluoroquinolones and TMP-SMX may be useful for empiric therapy in such cases (**Table 3.1**).[54,55] High resistance rates to fluoroquinolones in many areas may make these less appealing as empiric options, and adverse effects are a concern. High resistance rates are likewise a concern with TMP-SMX, and prior urine cultures may be helpful in determining if fluoroquinolones or TMP-SMX are likely to be effective.

Although robust clinical trials of oral cephalosporins such as cefpodoxime as initial treatment for cUTI in adults are lacking, in practice cephalosporins are used in many settings as step-down therapy, when ESBL-production is not a major concern.[55-57] When choosing an oral cephalosporin for cUTI, both oral absorption and urinary excretion may be relevant parameters (See dosing **Table 3.1**) for consideration. Observational studies suggest that third generation oral cephalosporins may be comparable to oral fluoroquinolones or TMP-SMX as step down therapy in patients with cUTI and gram-negative bacteremia.[55-57] However, such studies are conflicting on whether earlier generation cephalosporins (e.g. cephalexin), oral beta-lactams (e.g. amoxicillin and amoxicillin clavulanate), and cephalosporins with low bioavailability (e.g. cefdinir) are as efficacious as alternatives; these should be used cautiously and with optimized dosing.[58-61]

As an example, in one retrospective study that included patients who received cefdinir (which has low urinary excretion of only 13-23% and low oral absorption of only 25%) and a lower dose of cephalexin (500 mg every 8 hours), readmissions for UTI were higher in the beta-lactam group compared to those who received fluoroquinolones or TMP-SMX.[59]

Amoxicillin-clavulanate and cephalexin have potentially lower efficacy as demonstrated in multiple studies.[58,60] Additionally, we did not find substantial data supporting the use of ampicillin, cefadroxil, cefaclor, or cefdinir for cUTI. Ideally, a patient who receives any of these oral options as their initial empiric therapy would have a urine culture from a prior episode showing susceptibility to the agent chosen.[62]

Furthermore, trials of three days of beta-lactam antibiotics for acute cystitis in women (cefpodoxime, amoxicillin-clavulanate, cefadroxil, and amoxicillin) consistently found lower clinical and microbiologic cure in the beta-lactam recipients, in comparison to three days of ciprofloxacin or trimethoprim-sulfamethoxazole.[63,64] These trials provide indirect evidence that beta-lactams are not as effective for acute cystitis when used for the same duration as other classes of antibiotics; whether these results are generalizable to empiric use of beta-lactam antibiotics to treat complicated UTI is unknown. Another concern with treating cUTI with oral beta-lactam antibiotics is that standard dosing may not achieve adequate levels in the urine. For example, a retrospective cohort study found that 7 days of IV or highly bioavailable antibiotics was as effective as 14 days of antibiotic therapy for bacteremic cUTI; of note, the doses of beta-

lactams considered to be bioavailable were the following: amoxicillin 1000 mg orally every 8 hours, amoxicillin-clavulanate 875–1000 mg orally every 8 hours, or cephalexin 1000 mg orally every 6 hours.[65] Increasingly institutions are using higher dose regimens for oral beta-lactams and cephalosporins as step down therapy for Gram-negative bacteremia of urinary origin.[54,66]

The 2010 publication of the UTI guidelines on cystitis and pyelonephritis recommended a single dose of aminoglycoside or ceftriaxone at the initiation of oral antibiotics to treat acute pyelonephritis, if resistance to the oral agent was a concern.[26] This panel did not find any studies of single dose aminoglycoside as part of a combination treatment for cUTI in adults, but in practice one or two doses of an aminoglycoside are often used as a component of the antibiotic treatment for acute pyelonephritis when there is a concern for an ESBL-producing organism.[53] We identified one study of single dose ceftriaxone in non-pregnant adults; this study suggested that a single dose of IV ceftriaxone prior to switching to an oral cephalosporin was an effective strategy for women with pyelonephritis.[30]

Nitrofurantoin and oral fosfomycin are generally not appropriate choices for cUTI due to inadequate levels in tissue/bloodstream. If treating suspected bacteremia, the oral agent needs to achieve therapeutic levels in the bloodstream, which would preclude using nitrofurantoin and oral fosfomycin. Likewise, if treating pyelonephritis, nitrofurantoin does not reach adequate drug levels in the renal parenchyma and would not be an appropriate agent for an oral switch. Oral fosfomycin has been used in small studies to treat cUTI (including pyelonephritis), but multi-dose regimens are generally used and are inconsistent across the literature; the effectiveness and dosing of fosfomycin for cUTI needs additional study.[67,68] Oral fosfomycin has been used to treat chronic bacterial prostatitis but has not formally been evaluated in acute bacterial prostatitis trials.[69,70]

Table 3.1: Dosing of oral antibiotics for complicated UTI in alphabetical order

Drug	Oral absorption (%)	Urinary excretion (%)	Dose for patients with normal renal function
Amoxicillin-clavulanate	80 (amoxicillin)[71] variable (clavulanate)[72]	50-70 (amoxicillin)[71] 25-40% (clavulanate)[71]	875mg-125mg every 8 to 12 hours[58-61,66,73-76] Other regimens may be more effective[a]
Cefixime	50[77]	50[77]	400mg once daily[30]
Cefpodoxime	50[77]	80[77]	200mg to 400mg every 12 hours[55,61,78]
Ceftibuten	75-90[77]	73[77]	9mg/kg daily (children)[b] 400mg daily or 200mg every 12 hours (adults)[79,80]
Cefuroxime	52[77,81]	90[77,81]	500mg every 12 hours[61,82]
Cephalexin	90[77]	90[77]	500mg to 1000mg every 6 hours[54,58-60,66,73-75,83] Other regimens may be more effective[a]
Ciprofloxacin	70[84]	40-50[84]	500mg to 750mg every 12 hours [54,61,66,85,86]
Levofloxacin	99[87]	64-100[87]	500mg to 750mg daily[25,54,78,86]

Other oral beta-lactams (e.g. amoxicillin, cefadroxil, cefaclor, cefdinir)	Comparative clinical outcomes data vs highly bioavailable oral alternatives are more limited and/or discouraging; consider use with infectious disease pharmacist consultation if alternatives are not available.		
Trimethoprim-sulfamethoxazole	70-90[88]	84 (sulfamethoxazole), 66 (trimethoprim)[88]	800mg-160mg every 12 hours[61,85]
[a]Despite routine use of optimized dosing, the majority of studies comparing switch to oral beta-lactams versus fluoroquinolones or trimethoprim-sulfamethoxazole for cUTI have found inferior outcomes with oral beta-lactams when amoxicillin-clavulanate or cephalexin were the predominant oral beta-lactams being used. [b]Ceftibuten is the sole oral beta-lactam in this table with modern randomized, controlled trial data for cUTI in both children in adults; however, while it produced comparable clinical outcomes versus trimethoprim-sulfamethoxazole in children, in adults relapses were higher with ceftibuten versus norfloxacin.			

10) Other antibiotics relevant to treatment of cUTI

IV Fosfomycin

Fosfomycin is an older antibiotic agent whose susceptibility testing is complicated, not easily amenable to automated methods, and rarely performed. In the U.S., fosfomycin susceptibility breakpoints for fosfomycin are established only for *E. coli* and for *Enterococcus faecalis*, and only for the oral formulation of fosfomycin. In practice, clinicians are often asked to determine whether fosfomycin would be an acceptable treatment for other urinary pathogens, such as *Klebsiella spp.*, but MIC breakpoints do not currently exist for non-*E. coli* organisms. Resistance to fosfomycin is increasing globally,[89] but as this antibiotic is infrequently used in the United States, many urinary organisms retain susceptibility.

Since intravenous fosfomycin is not available in the United States, fosfomycin is not an option for empiric therapy for most patients hospitalized for cUTI. Oral fosfomycin (fosfomycin trometamol) is a white powder administered as a sachet, to be dissolved in in water and then swallowed. This oral formation is available in the US and Europe and is used to treat uncomplicated UTI, or as step down therapy for patients with cUTI who are switching from IV medications to an oral agent and whose organism is known to be susceptible to fosfomycin. Fosfomycin's IV formulation is a calcium salt; this IV formulation is approved for cUTI for adults in Europe and Asia.

Summary of evidence for empiric use of IV fosfomycin to treat cUTI

The evidence on empiric use of IV fosfomycin for cUTI comes from two randomized, controlled trials which enrolled 607 evaluable patients. The open-label FOREST trial was conducted in 22 hospitals in Spain and enrolled patients with bacteremic UTIs caused by MDR *E. coli* (Sojo-Dorado 2022).[19] Although this trial was published in 2022, the 143 evaluable patients were enrolled from 2014-2018. The comparator in the FOREST trial was ceftriaxone or meropenem (if the causative organism was resistant to ceftriaxone), and the majority of patients transitioned to oral therapy after 5.5 days of IV therapy. Resistance to ceftriaxone among the

MDR *E. coli* was high, 57%. The ZEUS trial, published in 2019, enrolled 464 evaluable patients between 2016-2017.[21] Patients were randomized to seven days of IV fosfomycin versus piperacillin-tazobactam in a double-blind design, with no oral switch after IV therapy. All uropathogens were included in the ZEUS trial, and resistance to piperacillin/tazobactam was only 6.9%. Resistance to fosfomycin was not reported in the ZEUS trial and was an exclusion factor for the FOREST trial.

Benefits, Harms and Certainty of evidence

Treatment with IV fosfomycin likely leads to similar rates of clinical cure at test of cure in patients with cUTI versus treatment with comparator antibiotics. The overall clinical cure for fosfomycin was 92.2% vs 91.2% for comparators (RD: 0.9%; 95% CI: -3.6% to 5.5% / RR: 1.01; 95% CI: 0.96 to 1.06; moderate certainty of evidence).

Similarly, treatment with IV fosfomycin likely leads to similar rates of microbiological cure at test of cure in patients with cUTI versus treatment with the comparator antibiotics (RD: 6.4%; 95% CI: -1.9 % to 15.4% / RR: 1.10; 95% CI: 0.97 to 1.24). The evidence suggests that recurrence of infection at late follow-up may be comparable between groups, but this estimate is likely imprecise due to the small number of recurrences of infection documented. Of note, in the FOREST study, both relapses and reinfections were recorded, with reinfections defined as symptomatic UTI caused by a different strain of bacteria. Among the 132 patients in this analysis, 14 had relapse versus 8 with reinfection, demonstrating the very important principle that patients who are hospitalized for cUTI are at risk for another cUTI, regardless of initial treatment given.

Harms are an important consideration with IV fosfomycin, which is a salt and delivers 330 mg of sodium per gram of IV fosfomycin disodium, in comparison to the 65 mg of sodium per gram of piperacillin in the combination product piperacillin-tazobactam.[90] The IV formulation of fosfomycin contains significant sodium content that can exacerbate cardiac failure among individuals unable to tolerate large increases in volume. The evidence suggests that treatment with IV fosfomycin may lead to more non-serious adverse events than treatment with the comparator antibiotics (RD: 10.6%, 95% CI: 1.3% to 22.1% / RR: 1.33; 95% CI: 1.04 to 1.69), although this estimate only reflects the ZEUS trial.[21] In the ZEUS trial the main non-serious adverse events were mild and transient hypokalemia and elevated serum aminotransferases, both more frequently documented in the IV fosfomycin group. In the smaller FOREST trial, non-serious adverse events cannot be quantified between the two arms, but fosfomycin was discontinued among 6 patients due to adverse events (4 for heart failure); heart failure was reported among 6 patients treated with fosfomycin, all older than 80 years of age.[19]

Other considerations

Other considerations specific to IV fosfomycin include that the IV formulation is not available in the United States, and susceptibility testing of fosfomycin is not routinely conducted nor reported.

Rationale for recommendation and implementation

The panel judged that IV fosfomycin is not a first line antibiotic for empiric treatment of cUTI due to lack of availability, difficulty in conducting susceptibility testing, and concerns about adverse events, particularly sodium overload and hypokalemia. However, if available, this drug

can be an alternative antibiotic to empirically treat patients with cUTI without risk factors for resistance to fosfomycin. Caution should be taken in treating patients with known, chronic heart failure with IV fosfomycin.

Colistin

No randomized clinical trials exist to support the empirical use of colistin in cUTI. However, colistin (the active form of the commercially available parenteral prodrug colistimethate sodium, also polymyxin E) is suggested by the IDSA guidance document on managing antibiotic resistant pathogens as an alternative agent for treating uncomplicated cystitis caused by carbapenem-resistant Enterobacterales or *Pseudomonas aeruginosa* with difficult-to-treat resistance.[5] Colistin is also mentioned as a potential treatment for UTIs caused by carbapenem-resistant *Acinetobacter baumannii*. Colistin can cause nephrotoxicity and should rarely be used as an empiric initial treatment for cUTI.. Polymyxin B should not be used to treat UTI because of its predominantly non-renal clearance.

Drugs that do not currently have FDA approval for empiric treatment of cUTI

Three antibiotics that were tested in randomized, controlled trials seeking FDA approval for a UTI indication did not succeed in receiving this approval. These three agents merit brief discussion, as it is possible that additional trials or worsening resistance will lead to their use in the future for cUTI. These three antibiotics are omadacycline, tebipenem, and sulopenem.

Omadacycline is a modified tetracycline that has increased activity against some tetracycline-resistant organisms.[91] Omadacycline is available both orally and intravenously and is FDA approved for treatment of skin and soft tissue infections and pneumonia. Although active against *E. coli*, omadacycline is not active in vitro against the cUTI pathogens *Morganella* spp., *Proteus* spp., and *Providencia* spp. Overcash et al. conducted a phase 1 trial of omadacycline IV and/or orally to treat acute pyelonephritis in women; 201 patients were randomized, and omadacycline was “not non-inferior” to levofloxacin (did not meet non-inferiority criteria).[92] Another trial of omadacycline (IV and oral) for uncomplicated cystitis in 31 women found that 65% reported nausea, with 31% reporting vomiting.[93]

Tebipenem pivoxil hydrobromide is an orally bioavailable carbapenem prodrug that is converted to the active moiety, tebipenem, by enterocytes. Tebipenem has broad-spectrum activity against multidrug-resistant gram-negative pathogens, including ESBL-producing Enterobacterales. Tebipenem was studied in a phase 3 trial of treatment of cUTI, with IV ertapenem as the comparator.[94] Both groups were treated for 7 to 10 days (up to 14 days if bacteremic), and the primary outcome was a composite “overall response” that required both clinical and microbiologic response. Overall 1,372 patients were randomized, and 868 were included in the microbiological intent to treat group assessed for the primary outcome. The composite success outcome was reached by 59% in the tebipenem group versus 62% in the ertapenem group, meaning that tebipenem was non-inferior to ertapenem. Clinical cure was high in both arms of the study, at 93% and 94%, for tebipenem and ertapenem respectively. However, the FDA did not issue an approval for tebipenem for treatment of UTI.

Sulopenem is a thiopenem (sulfur fused to 5-member beta-lactam ring) which is active against ESBL-producing and Amp-C beta-lactamase producing Enterobacterales (organisms resistant to third generation cephalosporins such as ceftriaxone).[95] Sulopenem has an IV and an

oral formulation. The oral prodrug, sulopenem etzadroxil, is co-formulated with probenecid to reduce renal clearance and increase systemic levels of sulopenem. A phase 3 trial in 1395 patients with cUTI (including pyelonephritis) randomized participants to received IV followed by oral sulopenem, versus IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate.[96] The primary outcome was a composite of clinical and microbiologic cure, and microbiologic cure was stringently defined as reduction of the original pathogen to < 10^3 colony forming units (CFU)/mL (in contrast to other trials using a <10^4 CFU/mL threshold for microbiologic cure). Overall, in the modified microbiologic intention to treat or mMITT population (patients with a baseline urine culture with $\geq 10^5$ of an Enterobacterales pathogen susceptible to sulopenem and ertapenem), sulopenem was not non-inferior to ertapenem, with composite outcome rates of 67.8% and 73.9%, respectively. Although clinical cure was 88% or higher in both arms of the study, the microbiologic response was lower in the sulopenem arm than the ertapenem arm (71.2% versus 78.0%). The difference in outcomes between the two treatment arms was driven primarily by presence of asymptomatic bacteriuria in the sulopenem-treated group at test of cure (day 21). Closer examination of the microbiologic failures revealed that oral ciprofloxacin was better at eliminating Enterobacterales from the urine than oral sulopenem, provided that the organisms were susceptible to fluoroquinolones (4.7% microbiologic failure with ciprofloxacin versus 21.8% with sulopenem). The results of this trial highlight the potential dichotomy between clinical cure and microbiologic response and raise the question of the clinical significance of finding bacteriuria at the test of cure visit.

Other Considerations

Antibiotic stewardship considerations

In light of antibiotic stewardship principles (i.e., “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” [per IDSA guidelines]),[97] we advocate for the appropriate use of more narrow-spectrum antibiotics in patients without specific risk factors for infection caused by resistant pathogens. One meta-analysis reported that the incidence of *C. difficile* infection could be reduced by lowering exposure to ‘high-risk’ antibiotics, defined as clindamycin, fluoroquinolones, and cephalosporins, monobactams, and carbapenems.[98] For empiric treatment of cUTI, avoidance of antibiotics with a broad spectrum of activity when an agent with narrower spectrum of activity may be appropriate is aligned with principles of antibiotic stewardship. Empiric antibiotic choice always involves weighing antibiotic stewardship concerns versus the risk of inappropriate initial antibiotic choice.

Patients’ values and preferences

This guideline recommendation focuses on which antibiotics to choose at that critical point at which the patient with cUTI presents for care and the causative organism has not yet been identified (empiric antibiotic choice). Empiric antibiotics typically are continued for up to 72 hours before being replaced with tailored antibiotics based on culture results and other emerging data. In that context, avoiding mortality by choosing initially appropriate antibiotic therapy is the most important outcome. When expected mortality is low, consultation with the patient representatives participating in this guidelines panel further supported that treatment (whatever the choice of empirical therapy) should mainly focus on achieving clinical cure. If clinical cure is expected to be similar between different treatments, additional considerations

include antibiotic-associated adverse events, decreasing the risk of recurrence of infection, and avoiding readmission to hospital. Reducing the length of hospitalization and facilitating the ease of administration were considered important, but the choice of antibiotics by itself was not a driving factor in their decision-making process.

Costs, Resources, Feasibility and Equity

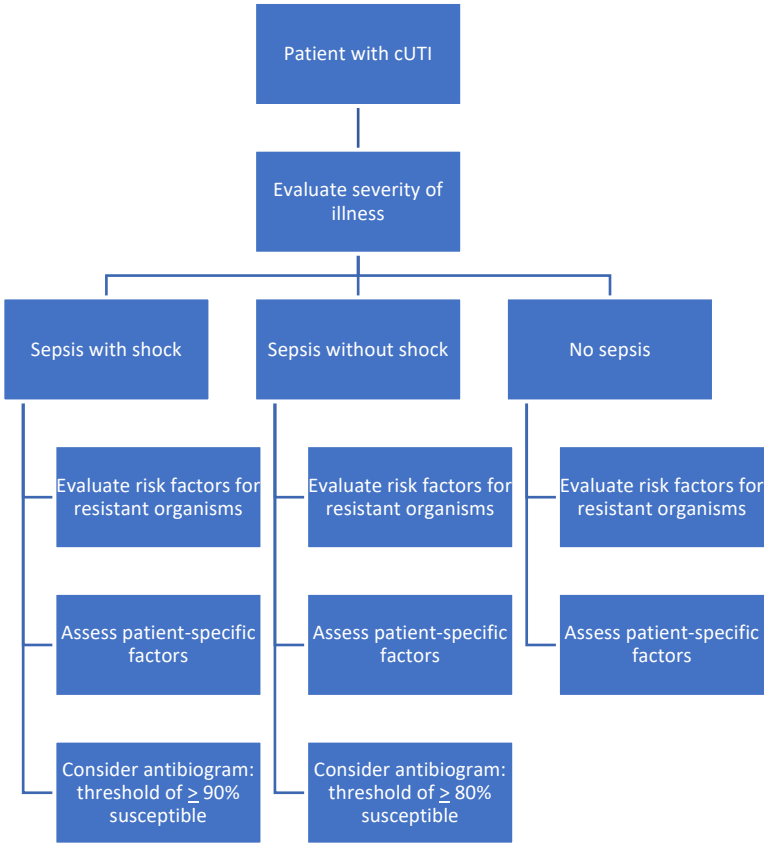
It is not possible for the guidelines panel to offer nationally generalizable direct comparisons of cUTI antibiotic costs because (at least in the United States) these costs vary widely based on the drug wholesaler and their contracts with individual pharmacies and institutions. That said, at the time of development of these recommendations, the average wholesale prices reported by the drug cost analysis tool Medi-Span (https://www.wolterskluwer.com/en/solutions/medi-span) suggests the antibiotics studied for cUTI can be categorized into three cost groups: low, medium, and high. Levofloxacin and ceftriaxone can be considered low-cost, with daily costs ranging from about $1 to about $50. Piperacillin-tazobactam and the carbapenems can be considered medium cost, with daily costs ranging from about $15 to about $150. Plazomicin, cefiderocol, and the novel cephalosporin and carbapenem beta-lactamase inhibitor combinations can be considered high-cost, with daily costs ranging from about $500 to $1500.

Thus, the potential excess cost of a 7-day course of cUTI treatment with agents other than levofloxacin or ceftriaxone is on the scale of a few hundred to a thousand dollars for piperacillin-tazobactam or the carbapenems, or several thousand to ten thousand dollars for the novel agents. Additionally, we consider that all of these antibiotic agents are given IV except for levofloxacin and ertapenem (which have oral and IM formulations, respectively), and thus would at minimum incur additional costs in the hundreds to thousands-dollar range for administration of outpatient parenteral antibiotic therapy (OPAT). Finally, we note that all of these agents other than levofloxacin, ceftriaxone, ertapenem, and plazomicin have every six hour or every eight hour dosing schedules, and so if given with on-label dosing could require the excess costs of extended hospitalization or nursing facility stay, likely in the several thousands to ten thousands of dollars range.

B. Process to Guide Empiric Antibiotic Choice for Complicated UTI

To optimize the selection of empiric antibiotic therapy for patients with suspected complicated UTI, we propose the following four step approach (**Figure 1.1**): 1) assess the severity of illness (for initial prioritization of empiric antibiotic therapy), 2) consider patient-specific risk factors for resistant uropathogens (for optimization of coverage), 3) evaluate other patient-specific considerations (to reduce the risk of adverse events), and 4) for patients with sepsis, consult a relevant local antibiogram if available (to further improve the likelihood of giving appropriate empiric therapy in septic patients).

Figure 1: Four-step approach to choosing empiric antimicrobial therapy for cUTI



This approach starts with the most important issue—the patient's severity of illness—and then takes into consideration the patient's risk factors for having a pathogen resistant to specific antibiotics or antibiotic classes, as well as practical issues such as antibiotic allergies. Finally, and only for patients with sepsis related to cUTI, the local antibiogram may have a role in helping the provider avoid inappropriate empiric antibiotic therapy if it is recent and relevant to the patient under consideration. The antibiogram is the last of the four recommended steps, as the evidence that using a facility's antibiogram to guide antibiotic prescribing for individual patients improves outcomes is very uncertain. Choosing which organism to focus on in the antibiogram is also a challenge in empiric decision making. The most relevant organism is suggested by the prior urine culture, if available. If not, *E. coli* is the default organism.

STEP 1: SEVERITY OF ILLNESS (initial prioritization of empiric antibiotic therapy)

In patients with suspected cUTI (including pyelonephritis), should selection of empiric antibiotic therapy be guided by severity of illness?

Recommendation:

I. For patients with suspected complicated UTI (including pyelonephritis), we suggest that the selection of empiric antibiotic therapy be initially guided by the severity of illness, specifically by whether the patient is in sepsis or not (*conditional recommendation, very low certainty of evidence*).

Remarks:

-Sepsis is defined per the Sepsis-3 Task Force as life-threatening organ dysfunction caused by a dysregulated host response to infection. These patients can be identified by SOFA score increase of 2 points or more, reflecting an in-hospital mortality greater than 10%, or presumptively identified with screening tools such as qSOFA or SIRS.[6,99]

The panel judged this clinical question to be the most important to guiding cUTI recommendations, especially after acknowledging that populations enrolled in randomized, controlled trials of empiric antibiotic choice have lower baseline mortality than general cUTI patient populations. Clinical practice is to use broader spectrum antibiotics in sicker patients (with the assumption that giving broader antibiotics means the empiric antibiotics are more likely to be effective against the pathogen). Quantifying the downstream impacts of choosing the wrong initial empiric antibiotic was necessary to provide stronger evidence for this practice. To identify subpopulations in which inappropriate antibiotic therapy has a significant impact on mortality is critical as it is one of a few factors that can be modified. A literature search was performed to define the prognostic impact of inappropriate empiric antibiotic therapy (IEAT) in patients with cUTI.

Prognostic Impact of Inappropriate Empiric Antibiotic Therapy (IEAT) in cUTI

First, we explored the question of quantifying the impact of choosing inappropriate empiric antibiotic therapy for cUTI, stratifying by severity of illness. To summarize the findings, an increase in mortality was observed in patients at high risk of mortality with cUTI receiving IEAT, with a pooled adjusted OR of 1.56 (0.99 to 2.46), as compared to patients receiving appropriate empiric antibiotic therapy. Below we will detail how this estimate was achieved.

Methods

To estimate the prognostic impact of IEAT in patients with cUTI, our systematic review of the literature included studies published since 2000 and studying adults with cUTI, most of whom were admitted to a hospital. Studies meeting these criteria were included if they reported the effect of IEAT on 30-day mortality or in-hospital mortality using a multivariate analysis. These studies were necessarily observational, as ethical considerations prohibit randomizing patients to appropriate versus inappropriate initial antibiotic therapy.

Empiric antibiotic therapy was defined as appropriate if the recovered pathogen in the urine culture (and/or blood culture) was susceptible in vitro to the antibiotics given before those culture results were available. For the analysis of the impact of IEAT, we focused on the outcome of mortality for two reasons: (1) mortality is the most patient-important outcome for decision making, and (2) mortality was the only outcome that was defined consistently across these studies. Note that mortality in these observational studies was much higher (above 5%) than in the randomized, controlled trials presented above which did not require a resistant pathogen as an inclusion criterion (less than 1%). Therefore, our models assessed the impact of IEAT on mortality, which was not possible using the RCT data.

Summary of evidence

Our systematic literature review identified eight observational studies reporting the impact of IEAT on mortality from cUTI after adjusting for other factors associated with mortality (Babich 2017, Esparcia 2014, Holmbom 2022, Korkmaz 2020, Ortega 2013, Righolt 2020, Rodriguez-Gomez 2019, Wiggers 2019).[100-107] (See **Supplementary Table B1.a** in Supplemental Materials). Three studies only included patients with bacteremia from suspected cUTI (Holmbom 2022, Ortega 2013, Wiggers 2019).[102,104,107] Two studies focused specifically on catheter-associated UTI (CAUTI) (Babich 2017, Ortega 2013).[100,104] These eight studies included a total 3,802 patients hospitalized with cUTI of whom 3,593 were further analysed. In most studies the average age of the patients was over 70. The eight included studies compared the effect on mortality of using an inappropriate versus appropriate empiric antibiotic therapy (IEAT versus appropriate empiric antibiotic therapy, or AEAT) based on subsequent urine culture in vitro susceptibility testing. IEAT was frequent, occurring in a mean of 27.5% across studies and ranging from 10.3%[102] to 50.8%.[100] All these studies were observational, and all but one[100] were retrospective. Clinicians' initial choice of empiric antibiotic therapy introduced the bias of confounding by indication, which was either partially or not accounted for at all in most studies. Confounding by indication in this context means that sicker patients likely received different antibiotics than less sick patients.

Estimate of the prognostic Impact of IEAT on mortality

To understand the impact of IEAT on mortality, we first looked at mortality in the patients that received AEAT, to provide an understanding of these patients' health outcomes under optimal antibiotic treatment conditions. The baseline mortality rate in patients receiving AEAT from these 8 studies averaged 14% (ranging from 5.8%[101] up to 34%). [106] Seven studies reported adjusted odds ratios for risk factors for mortality, including IEAT as one of the variables studied. (all except Rodriguez-Gomez 2019[106]). Combining these results, a statistically non-significant increase in mortality was observed in patients with cUTI receiving IEAT, with a pooled adjusted OR of 1.56 (0.99 to 2.46), as compared to patients receiving AEAT. Similarly, the only study reporting an adjusted hazard ratio (HR) for risk factors of mortality showed an adjusted HR of 1.99 (0.94 to 4.21) for mortality in patients with cUTI receiving IEAT.[106] Only one study utilized a propensity score to account for confounding-by-indication, and this study did not show an impact of IEAT on mortality (adjusted OR of 0.72 (0.39-1.32).[100] However, this study was exclusively in catheterized patients, overall mortality was very high (33%), and the diagnosis of CAUTI is often inaccurate.

Certainty in the evidence

The panel recognised that these estimates of the prognostic impact of IEAT on mortality in patients admitted for cUTI are very uncertain for various reasons, the most important being the serious risk of bias due to confounding by indication and residual confounding. Specifically, all cUTI studies of inappropriate antibiotic therapy were observational. Studies included in our estimate did not stratify for type of population, type of pathogen, or type of antibiotics. Reporting bias was also judged to be very likely. We limited the evidence base to studies that included IEAT in adjusted (multivariate) analysis of mortality, meaning that studies that found IEAT to be statistically insignificant in the unadjusted analysis and thus did not study IEAT in multivariate analysis were excluded from our evidence base.[108-110] This reporting bias likely caused an overestimation of the effect of IEAT on mortality. These studies were heterogeneous in terms of populations studied and statistical analyses performed. The multivariate analyses used different variables to adjust the odds ratio from one study to another. Thus, our estimated odds ratio is very uncertain.

Uncertainty in the diagnosis of cUTI in these retrospective studies also undermines the certainty about how much IEAT contributes to mortality. If a patient actually had another condition (particularly a non-infectious condition), the choice of antibiotics would not impact mortality. Alternatively, if patients are already very frail with high expected mortality or are presenting in later stages of sepsis, even appropriate empiric antibiotics may do little to improve their prognosis. In line with this theory, Esparcia 2014 reported that of the older adults admitted with cUTI, IEAT had a negative impact on 30-day survival only among those with a lower APACHE II score (less than 15).[101]

Finally, the panel was concerned about whether these findings are generalizable to cUTI populations at low risk of mortality (such as patients without sepsis, especially since studies not reporting mortality or low mortality rates were not included in this analysis. The panel acknowledges that when risk of mortality from cUTI is low, clinical failure may be more likely with inappropriate initial empiric antibiotic therapy. [35,111]

Other supporting evidence

Our landscape analysis of the literature found indirect evidence that supported our estimated odds ratio of 1.56 for mortality related to IEAT. Two meta-analyses addressed the question of whether inappropriate antibiotics (IEAT) were associated with mortality.[112,113] One of these studies included patients with UTI (Marquet 2015),[112] while the other did not specifically include UTI as a diagnosis, but many of the patients with gram-negative bacteremia may have had a urinary source (Paul 2010).[113] In both, IEAT was associated with an increase in mortality, and the pooled, adjusted odds ratios for mortality were 1.41 (95%CI: 1.22 to 1.61) and 1.60 (95%CI: 1.37 to 1.86) respectively. However, the studies that went into the meta-analyses were themselves observational and subject to the same biases discussed above for the studies of IEAT in patients with cUTI. Despite potential limitations in generalizing from studies including non-UTI patients, these meta-analyses further support our findings in patients with sepsis secondary to cUTI.

Other considerations

The urgency to provide appropriate initial empiric antibiotic therapy for patients with cUTI and sepsis or severe illness must be balanced against the potential harms of administering unnecessarily broad antibiotics. On the one hand, if every patient admitted to the hospital for

cUTI received antibiotics that would cover ESBL-producing Enterobacterales, multidrug-resistant *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci, the rate of IEAT would initially be very low. However, such non-discriminant overuse of antibiotics would lead to more antibiotic side effects for the individual patients, more collateral damage to patients' microbiomes, increased risk of *Clostridioides difficile*-associated diarrhea, and most critically, inevitable emergence of resistant organisms rendering the broad-spectrum regimens less effective and leading to excess mortality from infection in future episodes of care. The tolerable level of risk of choosing a regimen that may prove to be ineffective thus must be determined by the patient's severity of illness at presentation.

Rationale for recommendation

Based on this analysis, the panel judged that inappropriate empiric antibiotic therapy has differential impact on mortality in different subpopulations. In patients with cUTI at high baseline risk of mortality (with sepsis or septic shock), inappropriate empiric antibiotic therapy may increase mortality, but available data are very uncertain and likely overestimate the negative impact of IEAT. Nevertheless, indirect evidence also supports that selecting AEAT reduces mortality in patients with severe infections (sepsis with or without septic shock). In patients with cUTI with low baseline risk of mortality (without sepsis), choice of empiric antibiotics might be more likely to impact clinical failure rather than mortality (as excess mortality is unlikely), but our systematic review of the literature could not estimate excess clinical failure due to wide variation in definitions across studies.

Consequently, the panel judged that the selection of empiric antibiotic therapy be initially guided by the severity of illness (specifically by stratifying whether the patient is in sepsis or not). In other words, severity of illness can be used to guide choice of empiric antibiotic therapy for cUTI.

More specifically patients with sepsis (especially with septic shock) receiving early AEAT (which may require broad-spectrum antibiotics) may prevent (or avoid excess) mortality, and stewardship considerations may be deferred to definitive therapy. In patients without sepsis, antibiotic stewardship considerations may favor choosing the narrowest spectrum agent likely to provide an effective therapy (even if appropriateness of the empiric therapy remains uncertain).

Implementation issues (taking it to the bedside)

Defining sepsis at the bedside can be clinically challenging. The patient's severity of illness should be determined using the established SOFA score when possible. However, data to calculate SOFA score may not be readily available in some clinical settings. Screening tools such as SIRS criteria or qSOFA score may assist with presumptive identification of possible sepsis, though they have limitations of sensitivity and specificity.[6,114,115]

Note that much of the present evidence base for treatment is based on older definitions of sepsis such as SIRS criteria. SIRS criteria as a screening tool are more sensitive than specific for sepsis and do not correlate as well with severity of illness or outcomes as the Sepsis-3 SOFA criteria.[115] As such, applying this corpus of evidence to patient care in patients identified as 'septic' today requires translation.

STEP 2: PATIENT-SPECIFIC RISK FACTORS FOR RESISTANT UROPATHOGENS (optimization of coverage)

In patients with cUTI (including pyelonephritis), should selection of empiric antibiotic therapy be guided by patient-specific prior urine culture results and patient-specific risk factors for resistant uropathogens to optimize selection)?

Recommendations:

I. In patients with complicated UTI (including acute pyelonephritis), we suggest avoiding antibiotics to which the patient has had a resistant pathogen isolated from the urine previously (*conditional recommendation, very low certainty of evidence*)

> **Remarks:**
> **-**More recent urine cultures may be a better guide than more distant urine cultures.
> **-**The time frame for paired cultures (urine samples collected from the same patient at different occasions) varied, but the median was 3-6 months.

II. In patients with complicated UTI (including acute pyelonephritis), we suggest avoiding fluoroquinolones if the patient has been exposed to that class of antibiotic in the past 12 months (*conditional recommendation, very low certainty of evidence*).

> **Remarks:** More recent antibiotic exposure may be a better guide than more distant antibiotic exposure.

In clinical practice, clinicians' choices of empiric antibiotic therapy for cUTI are often influenced by perceived risk factors for having a resistant pathogen, or by results from a prior urine culture. The aim of this section is to identify patient-specific risk factors for having resistant uropathogens.

STEP 2-A: Prior urine cultures as a guide to empiric antibiotic therapy

In absence of evidence assessing the direct impact of selecting antibiotics based on prior urine culture results on clinical outcomes, our literature search initially focused on studies evaluating prior urine cultures' impact on appropriateness of antibiotic therapy in patients being treated for a current episode of UTI.

Prior urine cultures' impact on appropriateness of empiric antibiotic therapy

First, we explored the question of whether information on prior urine culture(s) should guide selection of appropriate empiric therapy for the current episode of UTI. We found that when empiric antibiotic therapy for the current UTI was concordant with the prior urine culture microbiologic data, the likelihood that the treatment would be effective against the uropathogen increased by at least 7-fold.

Methods

We included studies that had been published between 2000 and present (2023) based on patients presenting with any type of UTI and from any geographic location. These studies

needed to report on the impact of prior urine culture on appropriateness of empiric antibiotic therapy in patients treated for a current episode of UTI.

Summary of evidence

A total of 2 observational retrospective studies reported on the impact of prior urine culture on appropriateness of empiric antibiotic therapy in patients treated for a current episode of UTI.[62,116] Linsenmeyer at al. (Linsenmeyer 2015) studied a total of 101 patients corresponding to 126 episodes of multidrug-resistant organisms UTIs from three VA medical centers (from 2010 to 2013).[62] In the 95 episodes of MDR UTI (resistant to three or more classes of antibiotics) in which a prior urine culture was available within two years (of which 73% within 6 months), the same pathogen was identified in 92% of episodes. Similarly, Almomani et al. performed a retrospective study (Almomani 2020) in 483 patients corresponding to 693 episodes of UTI with paired urine cultures within 12 months (median interval between paired isolates was 3 months); in this study the first urine culture had to have an ESBL-producing organism as an inclusion criterion.[116]

Concordance between empiric antibiotic therapy and prior microbiological data was defined slightly differently in the 2 studies: Lisenmeyer 2015 defined concordance if EAT was active against all isolated Gram-negative bacterial pathogens of the index episode,[62] while Almomani 2020 defined concordance if the patient received proper therapy as per guidelines and previous microbiological data (i.e., as per the in vitro susceptibility of empiric therapy in ESBL-UTI).[116] In both studies, when there were numerous previous cultures, the culture with a profile with the most resistance was used to determine the classification of concordant EAT. Both studies stratified the association for different time frames, while Lisenmeyer 2015 also provided a stratification per classes of antibiotics.

Estimate on prior urine cultures' impact on appropriateness of empiric antibiotic therapy

When the choice of empiric antibiotic therapy for the index (current) infection was concordant with the prior microbiologic data, the likelihood of appropriateness of treatment against the uropathogen was increased by at least 7-fold (low certainty in the evidence). In summary, these two studies suggest that a prior urine culture can be helpful to optimize the appropriateness of empiric antibiotic therapy. One of the 2 studies also showed that a shorter duration between index and prior cultures was significantly associated with increased chance of ESBL-positive result in the current culture.

Certainty in the evidence

The panel recognised that these estimates on the impact of using prior urine culture on appropriateness of empirical therapy are uncertain due to the high risk of bias due to study design and due to serious concerns regarding residual confounding. Furthermore, this relationship is indirect and can be influenced by other factors that are difficult to measure, such as local practices in antibiotic choice. Lastly, whether appropriate empiric therapy improves clinical outcomes also remains unclear.[35,111]

Other supporting evidence

Our literature search also focused on other lines of supporting evidence: (1) predictive values of prior urine cultures in patients with paired urine cultures, and (2) prior uropathogen resistance to a specific antibiotic as a risk factor for current resistance. Refer to Supplementary Materials for methods and more detailed results. A summary of results follows.

1) Predictive values of prior urine cultures for current susceptibility or resistance

A total of 4 observational studies reported on the diagnostic test accuracy of prior urine culture to predict susceptibility or resistance to various antibiotics in patients who had at least two urine cultures available for review (MacFadden 2014, Dickstein 2016, Vellinga 2010 and Valentine-King 2023).[117-120] The timeframe of the prior cultures varied from within four weeks to more than 32 weeks. All these studies compared susceptibility phenotypes in the paired urine cultures, while one also reported on the likelihood of identifying the same organism.[118] All included studies reported on positive predictive value (PPV) and negative predictive value (NPV). In the context of paired urine cultures, PPV refers to the probability of a prior resistant culture to accurately predict future resistance. NPV refers to the probability of a prior susceptible urine culture to accurately predict future susceptibility.

Overall, having a prior uropathogen that showed susceptibility to a given antibiotic was better at predicting current susceptibility than a prior uropathogen with resistance to a given antibiotic was at predicting current resistance. NPV was higher than PPV across these studies (**Supplementary Table B2B.1**, Supplemental Materials). When looking at the predictive values of urine culture collected within the last 12 months, NPVs were generally above 80% (with a median NPV of 95% for fluoroquinolone, 72% for 3rd gen cephalosporins, 86% for TMP-SMX, and 98% for carbapenems), while PPVs varied greatly, ranging between 40 to 85% (with a median PPV of 76% for fluoroquinolones, 56% for 3rd gen cephalosporins, 59% for TMP-SMX, and 48% for carbapenems). When stratifying for specific antibiotics, NPVs were higher than PPVs in most cases.

We identified four factors influencing PPV and NPV across studies: prevalence of resistance,[117-120] time since prior culture,[117,118,120] intervening negative culture,[117,118] and antibiotic exposure between cultures.[118] To summarize, a prior urine culture can predict the susceptibility of the organism in the present urine culture, with the caveat that higher baseline prevalence of resistance, longer time between cultures, an intervening negative culture, and intervening receipt of antibiotics diminish the predictive value of prior cultures.

2) Prior uropathogen resistance to a specific antibiotic as a risk factor for current resistance

Three observational studies (all from the United States) reported the predictive value of identifying uropathogen resistance to a specific antibiotic in prior urine culture, after adjusting for other risk factors of resistance.[121-123] Only 20-30% of the patients in these study populations had a prior urine culture.[121,122] These studies only evaluated prior resistance as a predictive factor (rather than both prior susceptibility and resistance). The timeframe of the prior cultures varied from within 12 months[123] to within 6 years.[121,122]

Across studies and after stratifying for specific antibiotics, having a prior resistant uropathogen was an independent risk factor for identifying a uropathogen resistant to the same antibiotic in a UTI patient's present urine culture (**Table 4.1**). More specifically, adjusted ORs ranged 5.5-12.8 for fluoroquinolones,[121,122] 4.7-8.6 for TMP-SMX,[121-123] and 21.7 for third generation

cephalosporins.[122] Interestingly, two of these studies also showed that having more than one prior culture with the same resistance further increased the odds of identifying a uropathogen resistant to the same antibiotic.[121,122]

Table 4.1: Estimates of prior uropathogen resistance as a risk factor for current resistance

Antibiotics	**aORs of resistance (range)**	**Interval between cultures**	**Prevalence of resistance**
Fluoroquinolones[121,122]	-If one prior culture Cipro-R: 5.51 (3.33-9.16) to 12.8 (8.5-19.0) -If 2 or more prior culture Cipro-R: 6.1 (2.73-14.08) to 28.4 (13.2-60.7)	Up to 6 years	Cipro-R: 10.3% to 19.1%
Third generation cephalosporins [122]	-If one prior culture C3-R: 21.7 (7-69.2) -If 2 or more prior culture C3: 32.5 (5.06-126.4)	Up to 6 years	C3-R 6.9%
TMP/SMX[121-123]	-If one prior culture in the last 12 months TMP/SMX-R: 8.58 (3.92-18.81)	Last 12 months	TMP/SMX-R 20.3%
	-If one prior culture TMP/SMX-R: 4.7 (3.5-6.5) to 4.78 (2.87-8.07) -If 2 or more prior culture TMP/SMX-R: 5.4 (3.1-9.4) to 6.66 (2.85-17)	Up to 6 years	TMP/SMX-R 19.4%to 25.6%
aOR: adjusted odds ratio; R: resistant; Cipro: ciprofloxacin; C3: third generation cephalosporins; TMP/SMX: trimethoprim/sulfamethoxazole			
Limitations: For studies reporting on the predictive value of prior uropathogen resistance as a risk factor, many of the patient did not have a prior urine culture. The subpopulation of patients who had a prior culture (with or without a specific resistance) might be different from the rest of the cohort who did not have a prior urine culture (i.e. population with recurrent UTI vs first episode of UTI), which could have introduced a selection bias. Furthermore, most studies were aiming at creating pragmatic algorithms which included and adjusted for a limited number of risk factors in analyses, making these estimates more prone to residual confounding.			

Other considerations

The paired culture studies showed that NPV (susceptibility in the first culture) was predictive of susceptibility, much more strongly than PPV (resistance in the first culture) was predictive of resistance. However, the larger body of literature looked at risk factors from the patient's past that predict current resistance, not susceptibility. When a clinician is choosing an antibiotic, the cognitive choice is most commonly structured as which antibiotics to avoid because of potential lack of effectiveness. Therefore, these recommendations concerning use of prior cultures to guide therapy are structured around prior resistance, to make them more feasible to implement.

Rationale for the recommendation

Based on this evidence, the panel suggests avoiding antibiotics to which the patient has had a resistant pathogen isolated from the urine previously, but also recognized that other factors may influence this decision; for example, a recent culture may provide stronger evidence to support this decision, particularly when results are discordant between more distant cultures and a more recent culture. We did not find literature on predictive value of prior blood culture for current urine culture susceptibility profile, but the panel believes that susceptibility could be extrapolated from a prior blood culture collected during a cUTI.

Implementation issues (taking it to the bedside)

Many patients visit more than one healthcare system. Therefore, prior urine culture reports may not be available to the clinician treating the current episode of cUTI. In some cases, a discharge summary or verbal report upon transfer of the patient to the emergency department may simply note that the patient had a prior ESBL producing organism, without providing specific culture results. Such information can probably be given the same weight as a prior urine culture with an ESBL-producing organism. Verbal reports of "ESBL positivity" or "KPC" can be a clue to the likely pattern of resistance to multiple antibiotics. Urine cultures in real-life scenarios can have multiple organisms or contaminants, potentially obscuring the true pathogen. Patients may have serial urine cultures that show different organisms with different resistance patterns. In such cases the overall resistance phenotype, or conversely, the overall susceptibility phenotype, is probably a reasonable guide for empiric antibiotic choice. Unfortunately, if the prior organisms have been treated with antibiotics, the possibility of a new organism emerging is real. Some patients, due to prior antibiotic exposure, may develop infections with less common pathogens (e.g., *Pseudomonas aeruginosa* or *Enterococcus spp.*), though predicting which patients will develop UTI with these pathogens is beyond the scope of these guidelines. Patients with indwelling urinary catheters (transurethral or suprapubic) and/or neurogenic bladders have often been heavily treated for Gram-negative urinary organisms in the past and are likely to be carrying resistant Gram-negative organisms or non-Enterobacterales organisms.[124]

STEP 2-B: Risk factors of resistance to a specific antibiotic class as a guide to empiric antibiotic therapy

To identify patient-specific risk factors for resistant uropathogens that could help guide the selection of appropriate empiric therapy, we performed a systematic review of the literature aiming at identifying the strongest predictor(s) of specific resistance(s) or resistance pattern(s), such as FQ, ESBL or TMP-SMX.

Methods

Our criteria for inclusion were that the study had to have been published between 2000 and present (2023) and reported on North American populations (United States, Canada, and Mexico), as risk factors of antibiotic resistance will vary depending on the local epidemiology. Included studies had to report on adults with cUTI, meaning that studies that were based on laboratory data only (i.e. without a confirmed clinical diagnosis of UTI) were excluded. Many of the studies also included adults with uncomplicated UTI, but the study was included as long as

some of the patients had been diagnosed with cUTI. Studies needed to report on risk factors for resistance among common Gram-negative uropathogens. Finally, studies meeting these criteria were included only if they reported adjusted relative risks using a multivariate analysis.

For selected risk factors to be useful in a clinical practice (i.e. develop actionable recommendations based on these risk factors), these needed to be **specific to an antibiotic class (e.g. FQ-R, ESBL and TMP/SMX-R)** rather than general (**e.g. MDR**). For example, if residing in a nursing home is associated with an increased risk of resistant uropathogens but not specifically to an antibiotic class, then this risk factor is descriptive and too general to recommend avoiding a specific antibiotic class when selecting empiric antibiotic therapy. Many factors (e.g. nursing home residence, presence of indwelling urinary catheters) are associated with risk of having a multidrug resistant organism. These factors may all relate to the common pathway of healthcare exposure and thus more antibiotic exposure. Nevertheless, knowing that the patient is at higher risk for having a multidrug resistant organism does not guide the clinician at the moment of choosing specific empiric antibiotics.

Due to the expected limitations intrinsic to the identified literature (see below), the panel judged that only risk factors that were **strong predictors** should be reported in our final analysis. We defined strong predictor as an independent risk factor (reported in at least 2 included studies) with an adjusted odds ratio (aOR) consistently greater than five across the included studies. We chose this threshold as one at which knowing a risk factor was likely to meaningfully alter post-test probabilities of resistance to a specific antibiotic and usefully inform antibiotic selection. All risk factors reported as independently associated with resistance to a specific antibiotic were considered for further analysis (see Supplemental Materials for additional details).

Summary of evidence

Our systematic review of the literature identified a total of 16 observational studies reporting on the various risk factors for having a urinary pathogen resistant to a specific antibiotic class in patients with cUTI.[39,123,125-138] Of these risk factors, only one was considered a strong predictor for a resistance to a specific antibiotic class: prior exposure to the same antibiotic (fluoroquinolones) in the last 12 months (**Table 5.1**).

Table 5.1: Independent risk factors of resistance to a specific antibiotic class

Risk factors	aORs of resistance	Timing	References	Strength of association
Risk factors of fluoroquinolones resistance				
Prior exposure to fluoroquinolones (in the last year)	4.62 (1.09-19.61) 15.73 (6.15-40.26) 30.35 (5.82-158.42)	Prior month	Khawcharoenporn 2012[130] Rattanaumpawan 2010[133] Killgore 2004[131]	Strong Predictor
	23.35 (8.20-76.85)	Prior 3 months	Shah 2017[135]	
	21.8 (3.7 – 127.1)	Prior 6 months	Cohen 2006[126]	
	7.6 (2.1-27.5) 13.16 (3.11-68.43)	Prior 12 months	Johnson 2008[39] Shah 2017[135]	
	1.95 (1.66 – 2.28)	Unclear	Rich 2022[134]	
Healthcare exposure (hospital or nursing	Nursing home 1.93 (1.22 – 3.07)	Current	Faine 2022	Weak Predictor

home in the last 3 months)	2.80 (1.02-7.25) 4.41 (1.79-10.88)	Current Current	Shah 2017[135] Rattanaumpawan 2010[133]	
	Hospitalisation 2.0 (1.0-3.9) 2.19 (1.31-3.64) 3.99 (2.38-16.30) 0.97 (0.87 – 1.09)	Each prior week of hospitalisation Prior 2 weeks Prior 3 months Past year	Johnson 2008[39] Kratochwill 2015 Rattanaumpawan 2010[133] Rich 2022[134]	
	Nosocomial 2.56 (1.31-5.02)	Prior 3 months	Khawcharoenporn 2012[130]	
Risk factors of resistance to TMP/SMX				
Prior exposure to TMP/SMX	2.36 (1.94-2.88) 2.58 (1.13-5.89)	Unclear Prior 12 months	Rich 2022[134] DeMarsh 2020[123]	Weak Predictor
aOR: adjusted odds ratio Strong predictor: independent risk factor (reported in at least 2 included studies) with an aOR consistently greater than five across the included studies; Weak predictor: independent risk factor (reported in at least 2 included studies) with an adjusted odds ratio aOR not consistently greater than five across the included studies				

Effect of prior fluoroquinolone (FQ) exposure on risk of FQ resistance

A total of 7 observational studies reported on prior fluoroquinolone use as an independent risk factor for identifying fluoroquinolone resistant uropathogens in patients with cUTI (Killgore 2004, Cohen 2006, Johnson 2008, Rattanaumpawan 2010, Khawcharoenporn 2012, Shah 2017, and Rich 2022).[39,126,130,131,133-135] Data collection in these published studies occurred between 1998 to 2019. The risk factor studied was fluoroquinolone exposure versus no prior fluoroquinolone exposure. Unfortunately, the time frame for prior exposure varied from 1 week to 12 months, and the nature of the exposure was not defined further in terms of dose or duration. See Supplemental Materials for additional details on the studied populations.

Overall, the adjusted odds ratio for prior FQ exposure ranged from 2.0 (1.7 – 2.3)[134] to 30.4 (5.8 – 158.4)[39,126,130,131,133-135] The pooled, adjusted odds ratio was 13.7 (8.4-22.4) (**Table 6.1**).[131] A dose response gradient was seen within one study that looked at two different time periods for fluoroquinolone exposure (prior 3 months: 23.4 (8.2-76.9) vs prior 12 months: 13.2 (3.1-68.4).[135] The literature suggested a strong relationship between prior fluoroquinolone exposure and having a fluoroquinolone-resistant organism when presenting with cUTI.

Table 6.1: Impact of prior fluoroquinolone exposure on the adjusted odds ratio for fluoroquinolone resistance UTI

Time frame for exposure	Adjusted odds ratio (aOR)	References
Prior month	4.6 (1.1-19.6) 15.7 (6.2-40.3) 30.4 (5.8-158 .4)	Khawcharoenporn 2012,[130] Rattanaumpawan 2010,[133] Killgore 2004[131]
Prior 3 months	23.4 (8.2-76.9)	Shah 2017[135]
Prior 6 months	21.8 (3.7-127.1)	Cohen 2006[126]
Prior 12 months	7.6 (2.1-27.5) to 13.2 (3.1-68.4)	Johnson 2008,[39] Shah 2017[135]

Other weak predictors of resistance to specific antibiotics

The literature also suggested a weak relationship between prior exposure to TMP/SMX and having an organism resistant to TMP/SMX in the current episode of cUTI.[123,134] However, TMP/SMX is not a preferred agent for initial empiric treatment of cUTI. We did not find any other predictive relationships between prior exposure to specific classes of antibiotics and having an organism resistant to those classes of antibiotics in a subsequent cUTI. The resistance risk factor literature may have had a bias towards detecting fluoroquinolone resistance, as more studies included fluoroquinolone exposure as a potential risk factor than to other antibiotic classes, and because fluoroquinolone resistance is more prevalent than resistance to some other classes (e.g. carbapenems).

Healthcare exposure to a hospital or nursing home within the prior three months was identified as a weak predictor of having a urinary organism resistant to fluoroquinolones.[39,127,130,132-135]However, healthcare exposure is likely linked to other risk factors for having a resistant organism (e.g. prior antibiotic exposure, comorbidities, presence of indwelling devices, and procedures).

Our systematic review of the literature (focused on studies from North America) did not identify an association between exposure to third generation cephalosporins and having an ESBL-producing uropathogen.[125,127-129,136-138]

Certainty in the evidence

The panel recognized that these estimates on the relative risk of prior exposure of fluoroquinolones on current fluoroquinolone resistance in patients with cUTI are very uncertain due to the high risk of bias due to study design as well as potential residual confounding. Interestingly, a dose-response gradient (i.e. an incremental increase in the risk of fluoroquinolone resistance with more recent exposure to fluoroquinolones) was observed in one study, which supports the biologic plausibility of prior fluoroquinolone exposure as a true risk factor. Nevertheless, our certainty in the evidence remains very low.

Of note, the value of a predictive factor depends on the baseline resistance rate, thus in a setting in which the prevalence of resistance to a specific antibiotic class is very low or very high, these predictors would not be as discriminative. Thus, these results seem generalizable to current North American practice but may vary with local epidemiology.

Rationale for recommendation

Based on this evidence, the panel suggests avoiding fluoroquinolones if the patient has been exposed to that class of antibiotic in the past 12 months, but also recognized that recent exposure (e.g. less than 3 months) may provide stronger evidence to support this decision.

Implementation issues (taking it to the bedside)

The treating clinician who has just diagnosed a patient with cUTI may not have information about the patient's prior antibiotic exposures, particularly if the patient visits more than one healthcare system or is coming from a long-term care facility. Even if the patient is within the same healthcare system, searching the electronic health record for prior antibiotics

can be time-consuming. Patients and their caregivers may not be able to identify specific antibiotics or the timeframe during which they were prescribed. Another important consideration is that the recommendation to consider fluoroquinolone exposure as a risk factor is drawn from literature in which the prevalence of fluoroquinolone resistance ranged from 10 to 45%. If local prevalence of fluoroquinolone resistance among urinary *E. coli* is higher than 45%, then the absence of prior exposure to fluoroquinolones cannot be taken as evidence that the patient's current urinary organism will be susceptible to fluoroquinolones.

STEP 3: OTHER PATIENT-SPECIFIC CONSIDERATIONS (prevention of possible undesirable events)

In patients with cUTI (including pyelonephritis), should selection of empiric antibiotic therapy be further guided by patient-specific considerations?

Recommendation:

I. In patients suspected of cUTI, empiric antibiotic therapy selection should account for patient-specific considerations (e.g. risk of allergic reaction, contraindications, or drug-drug interactions) to avoid preventable adverse events (*good practice statement*).

ΩzGuidelines cannot fully capture individual considerations. As a best practice, clinicians should take into account an individual patient's specific considerations. Such considerations should consider the patient's antibiotic allergy history, contraindications to receiving specific antibiotics, and potential drugs-drug interactions when selecting among the preferred and/or alternative options for empiric antibiotic therapy. Common sense suggests avoiding an antibiotic which the patient was taking when the current symptoms developed, or one which the patient took very recently.

STEP 4: ANTIBIOGRAM (tailoring empiric antibiotic therapy in septic patients)

In patients with cUTI (including pyelonephritis), should selection of empiric antibiotic therapy be further tailored by consulting an antibiogram?

Recommendations:

I. In patients with **sepsis** assumed to be caused by complicated UTI (including acute pyelonephritis), we suggest using an antibiogram to further tailor empiric antibiotic choice **only if** the antibiogram is local, recent, and relevant to the patient (*conditional recommendation, very low certainty of evidence*).

Remarks:

-An antibiogram is considered local if derived from the same healthcare facility, recent if based on data from the prior 12 months and relevant to the patient if based on organisms from a similar patient population.

-If an antibiogram is being used to further tailor empirical antibiotic choice, consider selecting an antibiotic for which 90% or more of the most relevant organism(s) are susceptible in patients in septic shock, or for which 80% or more of the most relevant organism(s) are susceptible in patients with sepsis without shock. These cutoffs are

based on modeling of increased mortality risk associated with inappropriate empiric antibiotics in sepsis and septic shock.
-Septic shock is defined by the Sepsis-3 Task Force as a subset of sepsis in which despite volume resuscitation, vasopressors are required to maintain blood pressure and serum lactate level is greater than 2 mmol/L, reflecting an in-hospital mortality greater than 40%.[6,99]

II. For patients with suspected complicated UTI without sepsis (including acute pyelonephritis), we make no specific recommendation about using an antibiogram to further tailor empiric antibiotic choice (*no recommendation, knowledge gap*).

Remarks:
-Patients who are not septic have a lower risk of mortality from cUTI (less than or equal to 5%) and initial inappropriate empiric antibiotic choice has little impact on mortality. Routine use of broader-spectrum agents in suspected complicated UTI without sepsis may drive antimicrobial resistance without substantial patient benefit.

Based on the review of the literature, the panel identified a lack of evidence about applicability of antibiograms to individual patients, particularly those with cUTI, and whether use of an antibiogram improves clinical outcomes. Therefore, modeling was performed to determine the impact of applying an antibiogram-based threshold for predicted susceptibility of a uropathogen to an empiric antibiotic choice, with the outcome of the modeling being excess mortality due to IEAT.

The panel judged that the use of an antibiogram for choosing empirical therapy for an individual patient with cUTI should be restricted to patients with sepsis for the following reasons: (1) The antibiogram's value in guiding antibiotic choice for an individual patient is unproven, particularly when the organism itself is not known. (2) Modeling for use of the antibiogram to avoid excess mortality due to inappropriate empiric antibiotic therapy (IEAT) was relevant only to patients with an expected mortality of 10% or higher. (3) Antibiograms need to meet certain standards to be useful, and the general practitioner is unlikely to know how the facility's antibiogram was constructed.

Modeling for impact of using antibiogram thresholds on excess mortality

Our analysis of eight studies that compared mortality outcomes with IEAT and AEAT found a pooled odds ratio of 1.56 increased mortality with IEAT (see IEAT section above). This estimate of 1.56 is likely an overestimate because studies that did not find IEAT to be a significant factor in mortality were not included in our modeling. The panel judged that a reasonable susceptibility threshold for choosing an antibiotic to use for a patient with cUTI and sepsis or septic shock should confer no more than a 1% risk of excess mortality due to IEAT. In other words, the panel judged that the tolerable level of excess mortality risk should be less than one per 100 patients treated. Using this odds ratio of 1.56, the threshold for avoiding 1% increased mortality in septic shock is to choose an antibiotic for which at least 90% of the relevant organism are predicted to be susceptible. If the patient is septic but not in shock, the threshold to avoid a 1% increase in mortality is to choose an antibiotic for which at least 80% of the relevant organism are predicted to be susceptible. See **Table S7** in the supplemental materials.

For patients with cUTI with a low baseline mortality (5%), the choice of empiric antibiotics might be influenced more by clinical failure than mortality (as excess mortality is so unlikely). Unfortunately, we judged that modeling for excess clinical failure would not be sound

because both the definition of clinical failure and the study populations varied substantially across studies. For example, one trial included mortality in the composite outcome of clinical failure, while another included microbiologic persistence in the outcome of clinical failure.

Other considerations when using an antibiogram to guide empiric antibiotic choice in individual patients

While patient-specific risk factors help define if a given patient may have a urinary organism that is resistant to one or more antibiotics, the local antibiogram may not necessarily apply to an individual patient.[139] For example, if a patient has recently been living in a different state, or recently traveled extensively in another country, the local hospital's antibiogram may not apply. If the patient is undergoing chemotherapy and has been hospitalized multiple times recently, the outpatient antibiogram may not be relevant, even if the patient is presenting for care in an outpatient setting. Antibiograms derived from hospitalized patients may not be relevant to primary care settings. Application of an antibiogram at the point of care can be difficult when the causative organism is not known. In a patient with recurrent infections or another recent infection, the patient's microbiological history and antibiotic exposure may provide more relevant information than a facility-wide antibiogram.[139] As an illustration of these concerns, a recent study in 127 VA facilities involving 2.2 million isolates of *E. coli* and *Klebsiella* species in 1 million patients found that a hospital-level antibiogram had limited ability to predict whether the patient's organisms would be resistant to specific antibiotics. [140] Another caveat is that evidence is lacking about whether use of an antibiogram in making empiric antibiotic choices improves clinical outcomes.[97]

Quality standards for antibiograms

The Clinical and Laboratory Standards Institute (CLSI) establishes standards for analysis and presentation of cumulative antibiotic susceptibility data.[141] Antibiogram data should be updated at least annually, and that only information from diagnostic cultures should be presented (rather than from surveillance cultures). At least 30 isolates of a species should be available during the time period covered if the organism will be presented in the antibiogram. Going beyond the CLSI basic standards, many facilities create antibiograms that are stratified by patient characteristics, such as sex and age, and/or are location-specific, such as antibiograms for the emergency department or intensive care unit.[139] The 2016 IDSA guidelines on implementing antimicrobial stewardship programs recommend developing a stratified antibiogram (by location, age, etc.). However, this recommendation is based on the idea that stratified antibiograms can expose important differences in susceptibility to guide facility-wide antibiotic recommendations rather than necessarily improving empiric antibiotic choice for individual patients.[97] We anticipate that the expansion of individualized risk prediction models may eventually supplant the use of facility-wide antibiogram to guide empiric antibiotic choice for a specific patient.[139]

Rationale for recommendation

Despite all the challenges in application of an antibiogram to an individual patient, the panel judged that a local, recent, and relevant antibiogram might help avoid excess mortality if used to guide empiric antibiotic choice for cUTI patients with sepsis. In patients with septic shock, the threshold for avoiding a 1% increase in mortality due to inappropriate empiric antibiotic therapy is to choose an antibiotic for which at least 90% of the isolates of the relevant organism are predicted to be susceptible. If the patient is septic but not in shock, the threshold to avoid a 1% increase in mortality is to choose an antibiotic for which at least 80% of the

isolates of relevant organism are predicted to be susceptible. These thresholds were established based on the current literature on inappropriate empiric antibiotic therapy and mortality, which yielded an odds ratio of 1.56 (95% CI of 0.99-2.46), indicating uncertainty related to the imprecision of this estimate. Newer literature and changes in this estimate may require recalculation of the thresholds; these guidelines establish a method for doing such calculations. (See **Table S7** Supplemental Materials). The increased mortality threshold judged by the panel as the acceptable upper limit (1% excess mortality, or 1 per 100 patients) was selected by consensus and is not informed by direct research on patient or clinician values. The applicability of these thresholds to real-world antibiotic appropriateness and their impact on clinical outcomes remains to be established and would be a suitable topic for future research.

For patients with suspected complicated UTI without sepsis (including acute pyelonephritis), the panel does not make a specific recommendation about using an antibiogram to further tailor empiric antibiotic choice. In patients whose risk of mortality from cUTI is less than or equal to 5%, initial inappropriate empiric antibiotic choice may delay recovery, lengthen hospitalization, or reduce the likelihood of clinical cure but has little predicted impact on mortality through our modeling.

Implementation issues (taking it to the bedside)

To guide antibiotic choice for a patient with sepsis from cUTI, the clinician would ideally be able to use a locally developed antibiogram that addresses the relevant patient population (e.g. ICU) and/or has a focus on urinary pathogens. Determining which organism to focus on in the antibiogram represents an additional challenge. The most relevant organism is suggested by the prior urine culture, if available. For example, if the prior urine culture had an ESBL-producing *Klebsiella* species, consult the antibiogram for effective therapy for ESBL-producing *Klebsiella*. In the absence of prior culture information, the panel suggests defaulting to the susceptibilities of *E. coli* when making an empiric choice of antibiotics for cUTI. The advent of rapid tests for antibiotic susceptibilities directly from urine may greatly reduce the role of the antibiogram in empiric antibiotic choice.

These guidelines are designed to avoid excess mortality through inappropriate empiric antibiotic therapy, but not to provide 100% coverage of all organisms that could possibly grow from the urine of a patient with cUTI or bacteremia of a urinary source. The healthcare clinician should apply individual judgment to considerations of whether the patient is likely to have a non-Enterobacterales organism (e.g. *Enterococcus spp.* or *Pseudomonas aeruginosa*) or a highly resistant urinary pathogen based on prior cultures and antibiotic exposures.

C. Selection of Definitive Antibiotic Therapy for Complicated UTI

In patients with microbiologically confirmed cUTI, should definitive effective antibiotic therapy be targeted based on the results of urine culture rather than continuing empiric broad-spectrum antibiotics?

Recommendation:

I. In patients with confirmed complicated UTI, we suggest selecting a definitive effective antibiotic with a targeted spectrum based on the results of urine culture (identification and susceptibility) as soon as these are available, rather than continuing empiric broad-spectrum antibiotics for the complete duration of treatment (*conditional recommendation, low certainty of the evidence*).

> **Comment:**
> -This recommendation places a high value on de-escalating antibiotic therapy based on culture results (stewardship considerations) while optimizing the effectiveness of therapy (improving clinical cure and reducing recurrence of infection). De-escalation may be less practical in cases of cUTI managed in the outpatient setting.

Balance of Benefits and Harms

Assuming that the balance of benefits (clinical cure, recurrence of infection) and harms (serious and non-serious events) as well as other considerations regarding costs/resources between targeted spectrum and broad spectrum-antibiotics are equivalent, then the remaining considerations mainly relate to stewardship issues.

Other considerations and stewardship issues

As mentioned above, the selection of definitive therapy should involve a consideration of the appropriate route of therapy (oral versus intravenous), the costs of different antibiotic treatment options, and the resources required to administer various antibiotic regimens (e.g. two IV antibiotics can cost the same per dose, but one may require administration three times per day, while the other is given once daily). Some antibiotics require therapeutic drug monitoring or pharmacist involvement to adjust dosing. Burden on patients and hospital staff are additional considerations. The antibiotic stewardship goal is usually to choose a more targeted antibiotic with the fewest collateral effects on the intestinal microbiota, when the susceptibility profile supports such a choice.

De-escalation (switching from broad to narrow agents) may not be practical in some situations, particularly when a patient with cUTI has been discharged with oral antibiotics to complete their treatment course. For example, the benefit of changing an oral third generation cephalosporin to a narrow-spectrum, first-generation cephalosporin for a few days of remaining therapy may be marginal. Also, calling patients to make this switch would require additional effort from the healthcare team, could confuse and inconvenience the patient, and might leave the patient with leftover antibiotics at home.

Rationale for recommendation

In patients with confirmed complicated UTI, we suggest selecting a definitive effective antibiotic with a targeted spectrum based on the results of urine culture as soon as these are available, rather than continuing empiric broad-spectrum antibiotics for the complete duration of treatment (conditional recommendation, low certainty of the evidence). This recommendation places a high value on deescalating antibiotic therapy based on culture results (stewardship considerations) while optimizing the effectiveness of therapy (improving clinical cure and reducing recurrence of infection). Whether a few days of a more targeted agent in comparison to a broad-spectrum regimen confer individual or global benefits in terms of antibiotic resistance is unclear, but tailoring the antibiotic regimen is a cornerstone principle of antibiotic stewardship.[142]

Implementation issues (taking it to the bedside)

Following up on the urine culture results is particularly important for patients managed for cUTI in the outpatient setting, to confirm susceptibility and switch to an effective antibiotic if needed.[143] A patient who has been diagnosed with and treated for cUTI may subsequently have a negative urine culture. When the clinician lacks culture evidence to guide antibiotic tailoring, the patient's clinical picture can be a guide. Patients who are improving on broad-spectrum, intravenous antibiotic therapy may be good candidates for transitioning to a more focused treatment regimen and for consideration of switch to an oral agent if resistant pathogens are not isolated.

Conclusions and research needs

Conclusions

Many of the classes of antibiotics approved to treat cUTI demonstrate similar efficacy as other classes of antibiotics in randomized, controlled trials. Bacterial resistance prevalence is always changing, and new antibiotics will be developed. In this context, the panel developed a four-step process for choosing empiric antibiotic therapy for cUTI that will potentially outlast the table of specific antibiotic choices. These steps are: 1) assess the severity of illness (for initial prioritization of antibiotics), 2) consider patient-specific risk factors for resistant uropathogens (for optimization of coverage), 3) evaluate other patient-specific considerations (to reduce the risk of adverse events), and 4) for patients with sepsis, consult a relevant local antibiogram if available (to further improve the likelihood of giving appropriate empiric therapy). The panel also developed a modeling approach to predict the impact of inappropriate empiric antibiotic therapy on mortality in cUTI that can be updated with new data as this emerges. However, the panel believes that the clinical principles of assessing severity of illness, considering the patient's individual risk factors, and evaluating which drug may suit the patient best will continue to be relevant to guiding treatment of cUTI.

Research needs

Whether or not microbiologic cure is a patient-relevant outcome is unclear. For the patients that have clinical cure but microbiologic failure (persistence of greater than 10^4 count-forming-unites/ml of bacteria in the urine at the test of cure time point), we know that such patients are at higher risk of clinical UTI by long term follow up. These patients presumably have asymptomatic bacteriuria at the TOC time point, since their clinical symptoms have resolved. What we do not know is whether treating the bacteriuria will reduce their risk of subsequent UTI.

To address this issue, a randomized, placebo-controlled, blinded trial would need to enroll patients who have been treated for cUTI/AP and who have clinical cure but microbiologic failure, and to randomize them to antibiotic treatment versus no treatment. Ideally the follow up period for recurrent UTI would be extended beyond 30 days after the last dose of antibiotics, out to one year, as antibiotic treatment could paradoxically increase the risk of recurrent UTI (rUTI) by disrupting the microbiome. Ideally this study would also perform molecular typing of the urinary organisms to see if rUTI is caused by the same or different organisms.

Little attention is given in the literature to determining whether men with febrile UTI have acute prostatitis. A systematic study of the signs and symptoms of prostatic involvement in men with UTI could help better define prostatitis as a clinical entity and thus facilitate detection of this condition in cUTI trials.

Another key research need is how to manage UTI in transgender adults. There is insufficient research on transgender and gender diverse individuals to inform guidelines and an urgent need for more research in this area. Nearly 1.6 million people ages 13 and up in the United States identify as transgender or have gender diverse experience. No clinical data exists to describe the epidemiology and risk factors for UTI in transgender and gender diverse individuals. We do not know if gender affirming therapy with hormonal treatment increases or decreases the risk of UTI. In addition to these epidemiology studies, future clinical trials should include gender-diverse samples and collect appropriately inclusive gender demographics on participants.[144]

The 2010 UTI guidelines on cystitis and pyelonephritis recommended one dose of aminoglycosides (or ceftriaxone) in patients with acute pyelonephritis who would otherwise be treated with entirely oral therapy, if there was concern for possibly having an organism resistant to the oral agent. This strategy should be explored in a RCT comparing a single dose or short course of aminoglycoside to placebo at the start of outpatient therapy for cUTI.

Finally, we need more data to define the role of the antibiogram in choosing empiric therapy for cUTI. Ideally this topic would be addressed in an RCT in which clinicians made empiric choices guided by an antibiogram or not guided by an antibiogram. The question of whether an antibiogram is relevant and helpful to choosing an empiric antibiotic treatment regimen for an individual patient with cUTI is an open one. The modeling strategy used in determining the antibiogram susceptibility thresholds to guide empiric antibiotic choice in cUTI patients with sepsis could be tested in a real-world study to determine the value of such thresholds at improving clinical outcomes. Research on how to use rapid molecular testing to identify urinary organisms and susceptibility at the point of care is needed, as injudicious use of such tests may drive overtreatment and overly broad antibiotic use.

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