Clinical Infectious Diseases

IDSA GUIDELINES

Clinical Practice Guideline by Infectious Diseases Society of America (IDSA): 2025 Guideline on Management and Treatment of Complicated Urinary Tract Infections: Timing of Intravenous to Oral Antibiotics Transition for Complicated UTI

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In patients who are being treated parenterally for cUTI, are clinically improving, can take an oral medication and for whom an oral option is available, should parenteral therapy be transitioned to oral rather than continued for the complete duration of therapy?

Recommendations

I. In patients with complicated UTI (including acute pyelonephritis) treated initially with parenteral therapy who are clinically improving, able to take oral medication, and for whom an effective oral option is available, we suggest transitioning to oral antibiotics rather than continuing parenteral therapy for the remaining treatment duration (*conditional recommendation, low certainty of the evidence*)

Comments:

- This recommendation places a high value on reducing avoidable intravenous catheter-related adverse events, costs, and resources, as well as taking into account practical aspects of antibiotic administration.
- The trials supporting this recommendation mostly excluded patients with indwelling urinary catheters, sepsis or septic shock, immunocompromised states, severe renal insufficiency, and functional or structural abnormalities of the urinary tract. Some patients in these subpopulations may need an individualized plan of therapy.
- An effective antimicrobial agent means that the antibiotic achieves therapeutic levels in the urine and relevant tissue and is active against the causative pathogen.
- Refer to Figure 1.2 for a stepwise assessment of the intravenous to oral switch and the duration of antibiotic therapy.

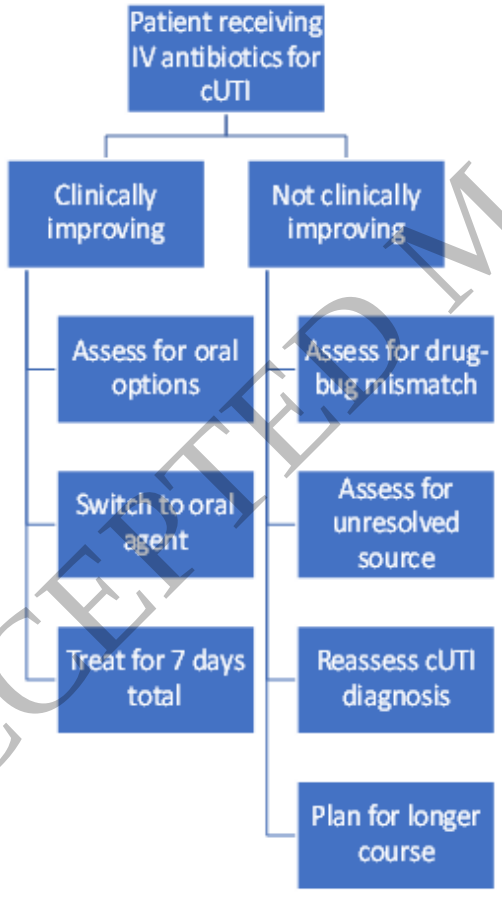
II. In patients presenting with complicated UTI (including acute pyelonephritis) and associated Gram-negative bacteremia treated initially with parenteral therapy who are clinically improving, able to take oral medication, and for whom an effective oral option is available, we suggest transitioning to oral antibiotics rather than continuing parenteral

therapy for the remaining treatment duration (conditional recommendation, very low certainty of the evidence).

Comments:

- The trials supporting this recommendation mostly included patients who were afebrile, hemodynamically stable, and had achieved source control (relief of any urinary obstruction) before transitioning to oral antibiotics.
- An effective antimicrobial agent for bacteremic patients means that the antibiotic achieves therapeutic levels in the bloodstream, urine, and relevant tissue and is active against the causative pathogen.
- Refer to **Figure 1.2** for a stepwise assessment of the intravenous to oral switch and the duration of antibiotic therapy.

Figure 1.2: Stepwise assessment of IV to oral switch and duration of antibiotic therapy



Abbreviations: IV=intravenous, cUTI=complicated UTI. Drug-bug mismatch means that the causative organism is not susceptible to the antibiotic prescribed.

INTRODUCTION

Antibiotic therapy is typically given for the shortest effective duration, and administered orally rather than intravenously when appropriate, in order to minimize adverse events related to therapy. An increasing number of clinical trials support early IV treatment with transition to oral therapy for infectious syndromes.[1,2] From a pharmacological point of view, antibiotic efficacy depends on the levels of the antibiotic obtained in serum and tissue, not the route of administration.[2] In practice, providers often switch from intravenous to oral antibiotics during the course of therapy for complicated UTI, once a patient is improving. We sought evidence about whether such transition impacts clinical outcomes of cUTI treatment versus continuing intravenous therapy. We also looked for information from clinical trials to guide the timing of this switch and appropriate circumstances for switching to the oral route.

From a practical perspective, an IV to oral switch, if equivalent in terms of outcomes, would be desirable because switching can reduce the need for intravenous access, complications from intravenous devices, nursing time and effort to administer the medication, volume of fluid and sodium given to the patient, duration of hospitalization, healthcare costs, and inconvenience to the patient.

Some patients with cUTI can be managed entirely with oral antibiotics in the outpatient setting. Please see a discussion of this topic in clinical question 1, under the section on "**Oral antibiotics for cUTI.**" Also see **Table 1.2** Dosing of oral antibiotics for complicated UTI.

SUMMARY OF THE EVIDENCE

Our systematic review of the literature, from January 2000 up to September 2024, identified four randomized, controlled trials (RCT) comparing transitioning to oral therapy to continuing parenteral therapy for the total duration of antimicrobial therapy for adults with complicated UTI (So-Ngern 2023, Monmaturapoj 2012, Malaisri 2017, and Concia 2006).[3-6]

Studied population: These four trials included 186 adult inpatients and outpatients from Asia and Europe, mostly female (82%). Although all enrolled patients had a presumptive or confirmed diagnosis of cUTI, the definition of cUTI varied between trials. Three trials included only patients with acute pyelonephritis,[3,4] while the third included only patients with cUTI associated with confirmed or presumed sepsis.[5] The Malaisri 2017 trial excluded bacteremic patients with UTI,[3] while bacteremia was present in 32% (n=15) of the patients in Concia 2006[5], 21% (n=17) of the patients in Monmaturapoj 2012[4], and 14% (n=3) of the patients in So-Ngern 2023.[6] The Malaisri 2017 trial[3] and So-Ngerm 2023[6] only included patients with UTI caused by extended spectrum beta lactamase (ESBL)-producing organisms, while the 2 other trials included UTI caused by all significant uropathogens.[4,5] The oral agents studied were fluoroquinolones (levofloxacin, prulifloxacin, and sitafloxacin) and cephalosporins (cefditoren pivoxil), which were compared to

either ertapenem, piperacillin-tazobactam, or ceftriaxone. The IV to oral switch was performed on day three or four of antibiotic therapy in patients whose clinical symptoms and laboratory parameters were improving and who could take oral medications. In three studies patients were no longer febrile at the time of switch, while the third study did not specify.

Pregnant and lactating women, as well as patients with sepsis or septic shock, immunosuppression, severe renal impairment, recurrent UTI within one month, structural abnormalities of the urinary tract (not further defined), or indwelling urinary catheters were excluded from most of these studies.

Studied comparison: The included trials compared transitioning to oral therapy against continuing parenteral antibiotics for the total duration of antimicrobial therapy.[3-6] Three studies used oral fluoroquinolones, and the total duration of therapy varied from 10 to 14 days. In these trials the patients enrolled had an effective oral option, meaning that the drug in the oral switch arm had good oral bioavailability, was excreted in the urine, and was active against the causative pathogen. Three of the four studies screened for susceptibility to antibiotic given in the oral arm, while one did not but was published before fluoroquinolone resistance became widespread.[5]

Although neither cefditoren pivoxil, prulifloxacin or sitafloxacin are currently available in North America, these trials have relevant information that bears on the IV to oral switch question and thus were included. Sitafloxacin and prulifloxacin are broad-spectrum oral fluoroquinolones, active against many Gram-positive, Gram-negative, and anaerobic bacteria, including strains resistant to other fluoroquinolones. Cefditoren pivoxil is a broad-spectrum, oral, third-generation cephalosporin. Cefditoren has a high volume of distribution, and 20-30% of the drug is excreted unchanged in the urine. The antimicrobial therapy varied among studies: (1) IV ceftriaxone followed by oral cefditoren pivoxil versus IV ceftriaxone;[4] (2) IV carbapenems followed by oral sitafloxacin versus IV ertapenem;[3] (3) IV empirical antibiotics followed by oral prulifloxacin versus IV ertapenem[6], and (3) IV levofloxacin followed by oral levofloxacin versus IV piperacillin-tazobactam, and in both arms patients also received amikacin for at least 3 days.[5] See the supplementary material (Characteristics of the studies).

Study design and risk of bias**:** All studies were judged at "unclear" risk of selection bias due to either: 1) lack of reporting of the method used to generate randomization, or 2) randomization of such a small sample that meaningful comparison of groups at baseline was not possible; therefore, whether randomization was successful at balancing important characteristics was unclear.

Three trials were open-label studies, meaning that participants, healthcare workers, and outcome assessors were not blinded to the treatment arms.[3,5] Unblinded studies can affect the outcomes that require subjective judgment, such as how clinical improvement or adverse events are measured and interpreted, thus potentially introducing detection and/or performance bias. All four studies were funded by industry, potentially introducing bias due to financial conflict of interest. See the supplementary material (Cochrane Risk of Bias).

Studied outcomes**:** The only patient-important outcome considered critical for decision-making was clinical cure (at end of therapy, EOT). Other outcomes considered important for decision-making included recurrence of infection, length of hospital stay, serious adverse events, IV catheter associated adverse events, and non-serious adverse events. No studies reported readmission rate or microbiological cure.

BENEFITS, HARMS, AND CERTAINTY OF THE EVIDENCE (COE)

Benefits and harms: Overall, transitioning from IV to oral therapy in the course of treatment for cUTI does not appear to reduce clinical cure or increase recurrence of infection, and transitioning may lead to potentially fewer intravenous catheter-related harms.

The evidence suggests that transition to oral therapy in patients with cUTI does not reduce clinical cure at EOT or TOC (risk difference or RD: 1.8%; 95%CI: -3.6% to 7.2%/ relative risk or RR: 1.02; 95% CI: 0.96 to 1.08; low CoE) as compared to patients continued on parenteral therapy for the full duration of treatment.

Transition to oral therapy may not increase recurrence of infection (RD: -2.0%; 95%CI: -2.9% to 6.1% / RR: 0.33; 95% CI: 0.04 to 3.05; low CoE), but this estimate is imprecise due to very few events and small sample size.

In the one study examining duration of hospitalization (Concia 2006),[5] transition to oral therapy might have reduced length of hospital stay (median 10.9 versus 17.2 days; absolute reduction of 6.3 days, 95% CI: 11.8 to 0.8 days fewer; very low CoE). This evidence is very uncertain due to imprecision (small sample size of 47 patients), risk of bias due to unblinded study design, and indirectness or lack of generalizability (i.e. the length of hospitalization reported in this study was directly influenced by the route of administration of antimicrobials since all patients received parenteral antibiotics in hospital). Despite this uncertainty, transitioning patients to oral antibiotics is very likely to shorten the duration of hospitalizations if receipt of IV antibiotics will delay hospital discharge.

Despite the available evidence being very uncertain, transition to oral therapy may reduce IV catheter related adverse events (RD: -4.9%; 95%CI: -11.5% to 1.7% / RR: 0.20; 95% CI: 0.01 to 4.04; very low CoE).

Each day of IV catheterization confers risks of adverse events related to the catheter. However, as IV treatment of cUTI is typically 7 days in duration or less, a switch between 3-7 days to oral therapy may not have appreciable benefit in terms of avoiding adverse events of catheterization in the individual patient. However, benefits may be realized in prevention of adverse events (such as infections) over a larger number of patients. An IV to oral switch can also reduce the volume of fluid and sodium given to the patient, but these outcomes were not studied in the included trials.

Transition to oral therapy may have little to no effect on serious adverse events (RD: -0.8%; 95%CI: -1.9% to 6.3% / RR: 0.65; 95%CI 0.11 to 3.88; low CoE) and on non-serious adverse events (RD: 1.0%; 95%CI: -2.1% to 16.7%/ RR: 1.35; 95% CI: 0.27 to 6.67; very low CoE). Imprecision due to few events and small sample size make these assessments uncertain.

Certainty of Evidence**:** The panel recognized that transitioning to oral antimicrobial treatment may provide the same potential benefits as continuing parenteral therapy (no reduction in clinical efficacy and no increase in recurrence of infection), may reduce length of hospitalization in certain clinical contexts, and possibly reduce adverse events (IV catheter associated adverse events, the benefit of which was judged by the panel to be small, especially with shorter duration of therapy). The panel agreed the overall certainty of evidence for transitioning to oral antimicrobial treatment compared to continuing parenteral therapy for the duration of treatment is low, mainly due to concerns with the risk of bias and imprecision in the estimates. However, IV to oral switch is common practice. See the supplementary material (Evidence Profile Table).

OTHER SUPPORTING EVIDENCE

Supporting evidence from trials studying similar treatment strategies: Two additional trials evaluated similar treatment strategies aimed at restricting the use of parenteral therapy in pre-selected populations. One of these trials looked at early switch versus very early switch (single dose IV), while the other looked at oral therapy throughout versus early switch. The very early switch trial was in women with uncomplicated pyelonephritis and compared the efficacy of a single dose of IV ceftriaxone followed by oral cefixime to standard treatment of IV ceftriaxone while awaiting culture results. Clinical response on day three or four of therapy was excellent and comparable between the two strategies (Sanchez 2002).[7] Another trial compared oral sitafloxacin therapy (throughout the course) to parenteral ceftriaxone with early transition to oral cephalosporins for 7-14 days in adults with complicated UTI or pyelonephritis. Oral therapy from the start was non-inferior to early transitioning to oral therapy, but these results might have been influenced by the difference in resistance rate to the study antibiotic within each arm (6.4% to sitafloxacin vs 30.4% to either ceftriaxone or cefdinir, respectively).[8] In conclusion, both of these studies support the idea that switching to oral antibiotics is effective in treating cUTI.

Supporting evidence from trials studying other aspects of cUTI treatment: The long-held belief that IV antibiotics are more effective than oral has been undermined by data from randomized, controlled trials of treatment for numerous serious infections, including osteomyelitis, bacteremia, and endocarditis (Davar 2022).[1] Transitioning to an effective oral antibiotic has become common practice for patients with cUTI showing clinical improvement. Most modern trials designed to either optimize the choice of empirical therapy or the duration of treatment for cUTI have permitted early transition to oral therapy. These trials reported excellent clinical outcomes similar to those in studies restricting treatment to parenteral therapy.

From trials studying optimal duration of therapy for cUTI: Our systematic review of the literature for clinical question 3 (duration of therapy for cUTI) looked at shorter treatment (5 to 7 days) versus longer treatment durations (10-14 days) for cUTI. All 10 trial protocols included clinical question 3 started treatment with either oral therapy or parenteral therapy but permitted transitioning to oral therapy (either as per protocol or as decided by the physician in charge). This analysis showed that shorter duration of effective antimicrobial therapy was not associated with worse outcomes in patients with cUTI, even when transitioning to oral therapy during the course of treatment. See summary of evidence for the clinical question on duration of therapy for cUTI.

From trials studying optimal choice of definitive antibiotic therapy for cUTI when transitioning to oral antibiotics: A randomized, controlled trial enrolling 97 women with cUTI which evaluated switch to oral fosfomycin versus oral ciprofloxacin after five days of IV therapy found clinical cure rates of 75% in both arms at 30-35 days post end of therapy.[9] Likewise, an oral switch study in 51 adults with cUTI (mostly pyelonephritis) who were switched to oral fosfomycin versus oral levofloxacin reported clinical cure rates of 84% and 86%, respectively.[10] In a study of IV fosfomycin versus beta-lactam antibiotics for bacteremic cUTI, 61 patients in the IV fosfomycin group were switched to oral fosfomycin, of whom 57 (93%) achieved clinical cure at the test of cure endpoint.[11] Of note, oral fosfomycin is not appropriate as an initial empiric treatment for cUTI, due to inadequate levels in tissue/bloodstream. Additionally, an observational cohort study of patients with gram-negative bacteremia from cUTI found that switch to oral fluoroquinolone or TMP/SMX had similar rates of recurrence within 60 days as completion of the full course of therapy intravenously.[12]

Supporting evidence from pediatric population: Two prior systematic reviews touched on this topic, although neither directly addressed the question in an adult patient population. A Cochrane review of routes of administration of antibiotics for severe UTI, published in 2007, included 15 studies, of which 9 focused on children, and 1 on pregnant women.[13] Only three of the six studies in adults were published after 2000. Studies were small and heterogeneous; only six addressed a specific comparison of switch (IV to oral) versus continuing IV therapy for the duration of treatment. Overall, no evidence was found that one route of antibiotic administration was less effective for the treatment of cUTI. However, patients who could not tolerate oral therapy were excluded from these trials. Voloumanou et al. published a systematic review in 2008 of early switch to oral versus intravenous therapy or late switch for patients hospitalized with pyelonephritis.[14] Of these eight studies, only two enrolled adults (rather than a pediatric population; both were conducted prior to 2000). Early switch was defined as occurring on days 1-4 of therapy; late switch was after 7-10 days of therapy. The antibiotics studied in these two trials were gentamicin, ceftriaxone, and cefixime. Overall, early switch to oral therapy was as effective as intravenous therapy for clinical and microbiologic cure rates, as well as preventing renal scarring in a pediatric population. While the populations included in these meta-analyses are not directly generalizable to the adult population, the concept that outcomes did not differ with route of administration is relevant.

SPECIAL POPULATIONS AND SPECIAL SITUATIONS

Presence of bacteremia

As our systematic review of the literature identified only four randomized, controlled trials of IV to oral antibiotic switch, this small number of trials did not permit post-hoc analyses. Across these four trials only 35 patients had bacteremia, so we were unable to formally stratify the analyses for presence or absence of bacteremia in cUTI.

A recent meta-analysis pooled the results of post-hoc analyses of 3 randomized, controlled trials (Yahav 2019, von Dach 2020, Molina 2022)[15-17] comparing 7 versus 14 days of antibiotics to treat uncomplicated Gram-negative bacteremia for cUTI patients who had become afebrile, were hemodynamically stable, and had appropriate source control by the time of randomization (Turjeman 2022).[18] All trials permitted step-down oral therapy as per the physician in charge. This analysis showed that shorter duration of effective therapy was not associated with worse outcomes in bacteremic patients with cUTI, even when many (or most) were transitioned to oral therapy. One of these 3 trials showed that transitioning from IV to oral was not associated with treatment failure in bacteremic cUTI patients, regardless of duration of antibiotic therapy (fixed 7-day course, fixed 14-day course, or duration guided by C-reactive protein) (von Dach 2020, personal communication). [16] In these three bacteremia treatment trials, the percentage of patients enrolled who had an ESBL-producing organism ranged from 6.9% to 18.7% (Von Dach 2020 and Yahav 2019).[15,16] The BALANCE trial further supports oral switch for patients with bacteremia in the context of a shorter overall duration of therapy.[19]

The evidence found did not specifically address the clinical scenario of a patient with cUTI or pyelonephritis who is treated with oral therapy in the emergency department or clinic and later discovered to have been bacteremic with a Gram-negative organism at the time of presentation. However, evidence suggests that such patients, if improving clinically, would not have to be switched to parenteral therapy simply because they were originally bacteremic. (Talan 2000, Von Dach 2020)[16,20,21]

Males with cUTI

We are unable to perform stratification for male patients only, as we could not access the original data from the majority of trials that included men and women. However, we believe that men with cUTI are equally eligible for IV to oral switch as women, with the caveat that an oral drug should be chosen that can penetrate the prostate in men with febrile cUTI. The panel is not aware of a validated approach to determine whether the prostate is involved in men with febrile UTI, so choosing a treatment that does penetrate the prostate is reasonable. Classes of UTI-relevant antimicrobials that have adequate prostatic penetration include fluoroquinolones and sulfonamides.[22] Some beta-lactam antibiotics have poor penetration into the prostate and prostatic fluid, although many cephalosporins do achieve therapeutic levels in the prostate. Nitrofurantoin does not appear to reach therapeutic levels in prostatic fluid and should not be used to treat acute

or chronic bacterial prostatitis.[23,24] Evidence for effectiveness of oral fosfomycin as a treatment for acute bacterial prostatitis is sparse.[25]

Resistant pathogens

The four trials mainly focused on transitioning from IV to PO when the oral therapy was considered to be effective for the infecting organism. Therefore, it is important to consider resistance rates to antibiotics among pathogens isolated in these trials. In the 2006 Concia study, no information was provided on resistance, but resistance to the two agents tested (piperacillin-tazobactam and levofloxacin) was not high at the time of that study.[5] In the 2017 Malaisri trial of sitafloxacin versus ertapenem, a urine culture with an ESBL-producing *E. coli* was required for enrollment.[3] All causative organisms isolated in the enrolled patients in this trial from Thailand were susceptible to carbapenems, and 94% were susceptible to sitafloxacin; only 25% were susceptible to ciprofloxacin or levofloxacin. Similarly, patients enrolled in the So-Ngern 2023 trial (prulifloxacin versus ertapenem) had to present with a UTI caused by an ESBL-producing organism which was susceptible to both studied drugs (with 76% of them being susceptible to ciprofloxacin and 100% to carbapenems).[6] The Monmaturapoj (2012) trial, also in Thailand, excluded patients with ESBL-producing *E. coli* or *Pseudomonas aeruginosa*, and having an organism susceptible to the study drugs (ceftriaxone and cefditoren pivoxil) was a requirement for inclusion.[4] In this study, 32% of *E. coli* strains were resistant to standard fluoroquinolones. In summary, 3 of these 4 trials provided effective therapy in both arms of the trial, supporting that IV to oral switch generally requires use of oral agent to which the causative pathogen is sensitive.

PHARMACOLOGIC ISSUES AND POTENTIAL CHOICES FOR ORAL SWITCH

Consider the following criteria when choosing an oral route of therapy for cUTI: (1) patient is clinically improving, (2) if applicable, source control has been achieved, (3) the patient can absorb oral antibiotics, (4) an oral regimen is available for the target pathogen that achieves adequate levels where needed (e.g., bloodstream if bacteremia present), and (5) there are no patient-level psychosocial or economic factors that would favor the IV route.[1] From a pharmacological point of view, the extent of tissue penetration is not necessarily determined by the route of delivery. Instead, an oral dose should be chosen that will achieve levels in plasma similar to those achieved through the IV route, which may require a higher oral dose. Gastrointestinal disorders that could preclude IV to oral switch include malabsorption, short bowel syndrome, ileus, severe diarrhea, motility disorders, vomiting, delayed gastric emptying, or reduced gut perfusion due to shock (Landersdorfer 2023).[2] Care should also be taken to avoid concomitant administration of certain medications, such as supplements (calcium, iron, magnesium) or sucralfate, that can reduce bioavailability of certain antibiotics (e.g. fluoroquinolones); some antibiotics' absorption may also be affected by food.

Nitrofurantoin and oral fosfomycin are generally not appropriate choices for cUTI and/or suspected bacteremia due to inadequate levels in tissue/bloodstream. Oral fosfomycin has been used in small studies to treat cUTI (including pyelonephritis), but its effectiveness needs to be confirmed in a larger study.[10,26] Oral fosfomycin has been used to treat chronic bacterial prostatitis but has not formally been evaluated in acute or chronic bacterial prostatitis trials.[27]

Patients with severe renal insufficiency may have either delayed clearance of some antibiotics or heightened clearance due to renal replacement therapy. Consultation with a pharmacist would be advisable in patients with severe renal insufficiency when planning an IV to oral switch for treatment of cUTI.

Ideally, the choice of oral step-down therapy can be guided by susceptibility testing of the causative pathogen, but often the organism has not been identified. Oral switch therapy in such cases is usually guided by the suspected urinary organism(s) and the patient's response to the empirical agent given. In other words, if the patient has improved while on ceftriaxone, switching to an oral third generation cephalosporin would be a reasonable choice. Commonly used oral switch options for cUTI include fluoroquinolones,TMP-SMX, and third generation cephalosporins (**Table 1.2**).[28,29]

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.[29-31] When choosing an oral cephalosporin for cUTI, both oral absorption and urinary excretion may be relevant parameters (See dosing **Table 1.2**) 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.[29-31] 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.[12,32-34]

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.[32]

Amoxicillin-clavulanate and cephalexin have potentially lower efficacy as demonstrated in multiple studies.[12,33] 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.[35]

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.[36,37] 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 using beta-lactam antibiotics as oral switch therapy 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.[38] Increasingly institutions are using higher dose regimens for oral beta-lactams and cephalosporins as step down therapy for Gram-negative bacteremia of urinary origin.[28,39]

Table 1.2: Dosing of oral antibiotics for complicated UTI (in alphabetical order)

Drugs	Oral absorption (%)	Urinary excretion (%)	Dose for patients with normal renal function
Amoxicillin-clavulanate	80 (amoxicillin)[40] variable (clavulanate)[41]	50-70 (amoxicillin)[40] 25-40% (clavulanate)[40]	875mg-125mg every 8 to 12 hours[12,32-34,39,42-45] Other regimens may be more effective[a]
Cefixime	50[46]	50[46]	400mg once daily[7]
Cefpodoxime	50[46]	80[46]	200mg to 400mg every 12 hours[29,34,47]
Ceftibuten	75-90[46]	73[46]	9mg/kg daily (children)[b] 400mg daily or 200mg every 12 hours (adults)[48,49]
Cefuroxime	52[46,50]	90[46,50]	500mg every 12 hours[34,51]
Cephalexin	90[46]	90[46]	500mg to 1000mg every 6 hours[12,28,32,33,39,42-44,52] Other regimens may be more effective[a]

Ciprofloxacin	70[53]	40-50[53]	500mg to 750mg every 12 hours [20,28,34,39,54]
Levofloxacin	99[55]	64-100[55]	500mg to 750mg daily[28,47,54,56]
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[57]	84 (sulfamethoxazole), 66 (trimethoprim)[57]	800mg-160mg every 12 hours[20,34]

[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.

OTHER CONSIDERATIONS

Stewardship considerations

Transitioning to oral therapy may permit earlier discharge, reducing potential exposure to nosocomially-acquired pathogens such as *C. difficile*, and may avoid placement of a central or midline catheter, reducing the likelihood of central-line (or midline) associated bloodstream infection. Evidence is not sufficient to mandate an IV to oral switch from a stewardship perspective.

Patients' values and preferences

The route of administration of antibiotics for cUTI needs to be individualized by patient preference. Our patient representatives commented that side effects of some oral antibiotics can be worse than the side effects of some IV antibiotics, and that responses are individualized.

Preference for receiving treatment at home and the perceived ease of taking oral antibiotics favor oral treatment. IV devices can be painful and limit mobility. Although some patients (and physicians) erroneously believe that IV antibiotics may be better or stronger, patients are likely to prefer oral antibiotics if efficacy is equivalent to that of IV antibiotics. [58-60]

Consultation with patient representatives participating in this guideline further supported that treatment (whatever the route of administration) should mainly focus on achieving clinical cure without increasing the risk of recurrence of infection and readmission to hospital. Reducing the length of hospitalization and facilitating ease of administration were considered important, but the route of administration alone was not a driving factor in their decision-making process.

Costs, Resources, Feasibility and Equity

While no specific studies evaluate the cost effectiveness of transitioning to oral therapy rather than continuing parenteral therapy for cUTI, the costs of administering oral antibiotics are significantly lower than either outpatient parenteral antibiotic therapy (OPAT) or inpatient administration of IV therapy. OPAT is associated with decreased costs compared to prolonging hospitalization for administration of those agents,[61] but OPAT costs are significantly higher than oral therapy in several infections.[62] Switching to oral antibiotics for bone and joint infections rather than OPAT can provide reductions in length of stay and costs.[63] In endocarditis, transitioning to oral therapy was also associated with a reduction in IV catheter complications.[64] Thus, the panel judged that moderate to large savings favor transitioning to oral therapy rather than continuing parenteral therapy for the completion of the treatment for cUTI.

The panel could not identify a scenario in which transitioning to oral therapy would not be more feasible or would not increase equity as compared to continuing parenteral treatment (either in hospital or through OPAT).

CONCLUSIONS AND RESEARCH NEEDS

The guideline panel suggests transitioning to oral antimicrobial treatment rather than continuing parenteral therapy in most patients with cUTI, including acute pyelonephritis, for those who are clinically improving, can take an oral medication, and for whom an effective oral option is available. The panel notes that a majority of the patients included in the studies supporting this recommendation were female and without indwelling urinary catheters. The oral antibiotics in three of the four studies were fluoroquinolones (including two not available in the United States, sitafloxacin and prulifloxacin). The evidence base included patients with both pyelonephritis and cUTI, although these are different infectious entities.

For patients with Gram-negative bacteremia associated with cUTI, the panel suggests transitioning to oral therapy in patients who are clinically improving, have adequate source control, who can take an oral medication, and for whom an oral option is available. Source control in this context

primarily meant relief of urinary obstructions; patients with abscesses in the genitourinary tract were generally not included in these trials.

Further clinical trials are needed to confirm the efficacy of the widely used strategy of giving one dose of an IV antimicrobial agent to patients with acute pyelonephritis, in addition to a course of oral antibiotics, in comparison to treating entirely with oral antibiotics. Very little is known about shorter course therapy for cUTI that does not involve fluoroquinolones, and fluoroquinolone therapy is becoming increasingly less relevant for cUTI as resistance rates increase.

Additional research into the safety of transitioning to oral therapy for certain subpopulations at higher risk of treatment failure or complications, such as patients with indwelling urinary catheters, sepsis or septic shock, immunocompromised status, severe renal insufficiency, and functional or structural abnormalities of the urinary tract is needed to ascertain whether this transition is safe and effective in these scenarios.

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