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REVIEW

Unmet Needs in Complicated Urinary Tract Infections: Challenges, Recommendations, and Emerging Treatment Pathways

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Abstract: While urinary tract infections (UTIs) are one of the most common types of infections globally, the wide variety of presentations and of severity of disease can make it difficult to manage. The definition for uncomplicated UTIs (uUTIs) is generally regarded as UTIs in healthy, non-pregnant women whereas all other UTIs are considered complicated. There is, however, a lack of consensus definition of complicated UTIs (cUTIs), leading to global differences in management. In addition, the patients who develop complicated UTIs generally have other comorbidities that warrant more urgent intervention. One of the biggest challenges in treating cUTIs is the rise of antimicrobial resistance (AMR). While there have been recent drug approvals for new antibiotic to treat these resistant organisms, a multidisciplinary approach, including regulatory frameworks, provider education and public awareness campaigns, is crucial to limiting unnecessary treatments for asymptomatic bacteriuria (ASB) and uUTIs that can ultimately lead to more severe infections.

Keywords: antimicrobial resistance, regulatory frameworks, catheter-associated urinary tract infection, clinical trial

Introduction

Urinary tract infections (UTIs) are some of the most common infections in both the outpatient and in other healthcare settings. UTIs have a wide spectrum of clinical presentations, from benign with mild symptoms to life-threatening. As such, UTIs have been stratified as either uncomplicated or complicated. While there is no standard definition, uncomplicated UTIs (uUTIs) are generally classified as UTIs in healthy, non-pregnant women whereas all other UTIs are categorized as complicated.[1] In 2011, UTIs accounted for over 400,000 hospital admissions with an estimated cost of $2.8 billion in the United States (US)[2] An updated 2018 survey found that UTI was included as a diagnosis in over 2.8 million discharge summaries and that complicated UTIs (cUTIs) accounted for over 625,000 hospitalizations yearly in the US, comprising 1.8% of all admissions.[3]

While there are many contributing factors to this increase in hospitalizations, one of the most obvious and alarming is the increase in antibiotic resistance. Antibiotic resistance accounts for nearly 700,000 deaths yearly due to drug-resistant strains in all types of bacterial infection[4] and costs the US healthcare system $55 billion in excess each year.[5]

There are many challenges with both diagnosing and treating UTIs. The lack of consensus definition, the wide variety of causative pathogens and patient populations, and the rise in antimicrobial resistance make treating these infections challenging. Through this review, we hope to better define and understand the unmet needs of complicated UTIs to help mitigate the personal and financial burden of these infections have not only on individual patients but also on the healthcare system.

Defining Complicated UTIs

UTIs were first categorized as uncomplicated and complicated in 1992 by the Infectious Disease Society of America (ISDA) and the European Society of Clinical Microbiology and Infectious Diseases, in an effort to standardize clinical trial participants. Defining cUTIs is crucial, as the categorization of the UTI often determines initial treatment regimen, which

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must balance patient disease and clinical status with the concern for development of antimicrobial resistance (AMR). For those with uncomplicated UTIs, *Escherichia coli* (*E. coli*) is by far the most common pathogen and as such oral treatment with trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin or fosfomycin are first-line therapies.[6] In cUTIs, other pathogens are increasingly common, and more broad-spectrum coverage often for longer durations must be considered in treatment.[1]

This definition of cUTIs, however, is incredibly broad and includes a heterogenous patient population requiring varying degrees of intervention (Table 1). In 2010, the European Association of Urology (EAU) and EAU Section of Infections in Urology (ESIU) proposed an alternative classification system.[7] This system classifies UTIs based on the clinical presentation of the UTI, the categorization of host risk factors and availability of appropriate antimicrobial therapy (Figure 1). The aim of this specific classification system is to appropriately prescribe empiric antibiotics, taking into consideration that those patients with cUTIs who may be at higher risk for being infected with highly resistant organisms.

Regulatory agencies internationally have similar definitions when providing guidance on drug development for cUTIs. The US Food and Drug Association's (FDA) definition as stated in a recent guidance on drug development for cUTIs is defined as "a clinical syndrome characterized by pyuria and documented microbial pathogen on culture of urine or blood, accompanied by local systemic signs and symptoms".[8] The FDA acknowledges that there are patient factors that increase the risk of developing cUTIs, including the presence of an indwelling urinary catheter, residual urine volume of greater than 100 milliliters (mL) after voiding (neurogenic bladder), obstructive uropathy, azotemia, or urinary retention. The primary efficacy endpoint in clinical trials as defined by the FDA should include clinical response (resolution of symptoms without development of new symptoms) and/or microbiological response (reduction of bacterial pathogen in culture $<10^3$ CFU/mL).

The European Medicines Agency (EMA) defines patients with cUTIs as having at least one complicating factor, such as indwelling urethral catheter, urinary retention, urinary obstruction or neurogenic bladder.[9] The EMA also sets a threshold for enrollment of different patients with different types of UTIs, such that patients with acute pyelonephritis and those with cUTIs should comprise at least 30% each of enrolled patients. Primary endpoints, similar to those in the US, include both clinical and microbiological improvement.

Challenges Associated with Diagnosing and Treating cUTIs
Common Pathogens

E. coli is the most common causative pathogen both in uncomplicated and complicated UTIs.[10] In order of prevalence after *E. Coli*, *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B Streptococcus (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*) and *Candida spp.* are common causes of uncomplicated UTIs. For complicated UTIs, the order of prevalence for causative agents, following *E. Coli*, is *Enterococcus spp.*, *K. pneumoniae*, *Candida spp.*, *S. aureus*, *P. mirabilis*, *P. aeruginosa* and GBS. Another study in hospitalized patients with cUTI found that *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *Enterococcus spp*, and *Enterobacter* as the most common pathogens, in order of

Table 1 Definitions of UTIs Among Various International Societies and Regulatory Agencies

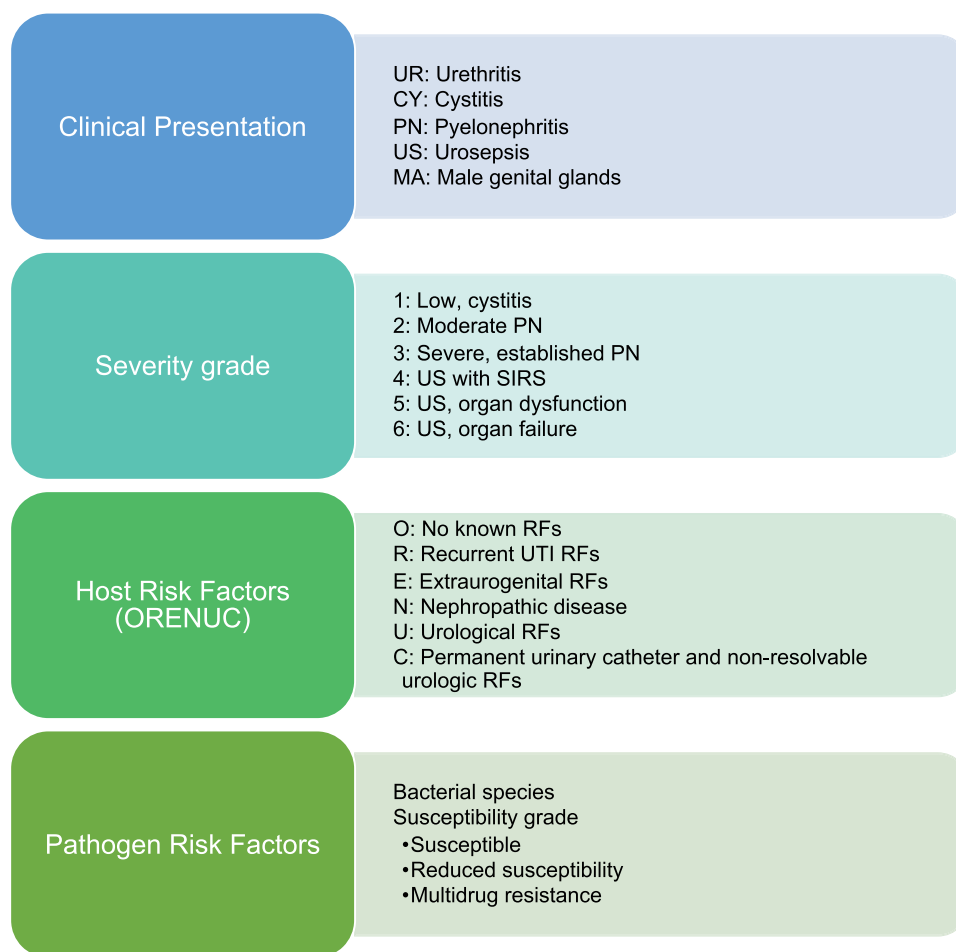| Organization	Definition of Complicated UTI
Infectious Disease Society of America (ISDA)[85]	Does not provide formal definition
American Urological Association (AUA)[86]	Infection associated with factors increasing colonization and decreasing efficacy of therapy
European Association of Urology (EAU)/EAU Section in Urology (ESIU)	Classification system that includes the clinical presentation, the severity assessment and any host or pathogen risk factors (Figure 1)
US Food and Drug Administration (FDA)	Clinical syndrome characterized by pyuria and documented microbial pathogen on culture of urine or blood, accompanied by local systemic signs and symptoms
European Medicines Agency (EMA)	UTI with complicating factor, such as indwelling urethral catheter, urinary retention, urinary obstruction or neurogenic bladder

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Clinical Presentation	UR: Urethritis CY: Cystitis PN: Pyelonephritis US: Urosepsis MA: Male genital glands
Severity grade	1: Low, cystitis 2: Moderate PN 3: Severe, established PN 4: US with SIRS 5: US, organ dysfunction 6: US, organ failure
Host Risk Factors (ORENUC)	O: No known RFs R: Recurrent UTI RFs E: Extraurogenital RFs N: Nephropathic disease U: Urological RFs C: Permanent urinary catheter and non-resolvable urologic RFs
Pathogen Risk Factors	Bacterial species Susceptibility grade •Susceptible •Reduced susceptibility •Multidrug resistance

Figure 1 The European section of infections in urology classification of UTIs. This classification includes the clinical presentation, the severity assessment and any host or pathogen risk factors (RF). This robust definition helps guide empiric antimicrobial treatment and duration.
Note: Data from Johansen TEB, Botto H, Cek M, et al. Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. Int J Antimicrob Agents. 2011;38:64–70. doi:10.1016/j.ijantimicag.2011.09.009.[7]

prevalence.[11] One of the added challenges, however, is that these patients can also have multiple causative pathogens, making treating these infections increasingly challenging.

Antimicrobial Resistance

In addition to the challenge of defining cUTIs, one of the biggest threats to the management of cUTIs is antimicrobial resistance (AMR). AMR is increasingly common in UTIs, however rates differ based on geographic region.[1] A review of worldwide antibiotic resistance found that 10 to 80% of pathogens were resistant to fluoroquinolones, 10 to 70% resistant to third-generation cephalosporins and 5 to 35% to carbapenems. Data shows that antimicrobial resistance is of high concern in gram-negative organisms.[12] A multicenter retrospective cohort study in south and eastern Europe found that multidrug resistant (MDR) UTIs were more likely to develop in men, where infections were acquired in a medical care facility, those with an indwelling catheter, those who had a UTI within the last year and those with prior antibiotic treatment within 30 days.[13] Resistance rates in those with urosepsis were higher than other clinical diagnoses of healthcare associated UTIs.[14] Because resistance rates and patterns vary based on region and treatment population, each facility should develop its own resistance surveillance program to appropriately tailor empiric regimens.

Resistance to pathogens often starts in the community with the treatment of ASB and uUTIs. A recent study of all antibiotic prescriptions in the US found an annual antibiotic prescription rate per 1000 population of 506, but only 353 were appropriate, demonstrating a need for improved stewardship in the outpatient setting.[15] A 2021 retrospective observational study analyzed

visits from 2015 to 2019 where antibiotics were prescribed for women with uUTIs.[16] They found that only 58.4% (26.2 million of 44.9 million visits) were concordant with ISDA guidelines and that fluoroquinolones, which have high resistance rates and are no longer recommended as a first-line therapy, were the most commonly prescribed, though there was decreased use over the four year analysis. In addition, they found that obstetricians and gynecologists and urologists had a statistically significant likelihood of prescribing concordant antibiotics as compared to all other specialties combined.

Clinician behavior also has a significant impact on antibiotic prescription in the outpatient setting. One study found that clinicians are motivated by risk aversion, where the imminent risk of infection outweighs the long-term risk of antibiotic resistance, action bias, where there is a tendency to take action even if not appropriate and patient satisfaction, where physicians feel compelled to prescribe antibiotics by patients.[17] Interventions using a multimodal approach, including engaging a quality improvement team, providing education to both prescribers and nurses, measuring performance data and providing feedback and adopting clinical decision tools and protocols, have been shown to decrease the treatment of ASB.[18] Another 2008 study found a 21% reduction in treatment of ASB in a geriatric university-affiliated hospital after education session with ward physicians.[19]

Another challenge is the decline of discovery of new antibiotics and one of the major barriers to development of antibiotics is the lack of investment. A guidance published by the FDA discussed how pharmaceutical companies are not incentivized to create antibiotics as these drugs have relatively low return as compared to other markets, such as oncology.[4] As such, there has been relatively little investment into creating novel antibiotics to tackle resistance, with less than 5% of venture capital investment in pharmaceuticals towards antimicrobial development.[20]

Special Patient Populations

While considering the virulence of the pathogen is important, often it is host factors that determines severity of disease. When diagnosing and treating cUTIs, it is critical to first underly the unique situations that may be present and impacting the clinical scenario.

Catheter-Associated UTIs

One of the most challenging groups of patients to treat for UTIs are those with indwelling catheters. Catheter-associated UTIs (CAUTIs) are the most common nosocomial infections both in the hospital and in long-term health facilities.[10] Short-term catheterization increases CAUTI risk by 3–7% with each day of placement and the risk of complications during hospitalization increases up to 80%. For those with long-term catheterization, risk of complication is nearly 100%.[21] CAUTIs are associated with increased morbidity and mortality and are the most common cause of secondary bacteremia.[10] The urinary catheter bypasses the normal host immune defense along the urethra, giving microorganisms that colonize the groin and perineum direct access to the bladder. In addition, the persistent irritation causes inflammation of the catheter in the bladder and the prevention of normal bladder contraction and micturition, which compounds the susceptibility for infection.[21]

The challenge with these patients is distinguishing asymptomatic bacteriuria (ASB) to a symptomatic CAUTI. A 2020 study found that biofilms on the catheters were found within several hours of catheterization and biofilms progressed as a function of indwelling time.[22] ISDA guidelines define CAUTI as "the presence of symptoms or signs compatible with UTI with no other identified source of infection along with ≥103 CFU/mL of ≥1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic or condom catheter has been removed within the previous 48 hours".[23] Signs and symptoms of infection include new onset fevers, rigors, altered mental status, malaise, lethargy, costovertebral angle (CVA) tenderness, acute hematuria, and/or suprapubic or pelvic pain or discomfort. In addition, the ISDA states that the "presence, absence or degree of pyuria should not be used to differentiate between ASB from CAUTI."[23] The Loeb criteria were created in 2001 to minimize overtreatment of ASB in long-term facilities.[24] These criteria recommend initiating treatment if at least one of the following are present: fever, new CVA tenderness, new onset of delirium or rigors. Although these criteria were published over 20 years ago, overtreatment of ASB continues to be a challenge.

Multiple studies have employed education programs to both nurses and physicians on the appropriateness of treating ASB in these patients. One study tested 169 medical residents and staff providers on the guidelines for treatment of ASB in patients with catheter, with an average knowledge score of 57.5%.[25] Another study from a long-term care facility of the Cleveland Department of Veterans Affairs educated nurses to discourage the collection of urine cultures in the absence of symptoms.[26] They found a sustained reduction in overall diagnoses and a reduction in total antimicrobial days of therapy that was maintained for 30-months

after the education session. Interestingly, this study illustrated that many of the ordering physicians were unaware of the ISDA guidelines for treatment of CAUTIs.

These patients specifically have high rates of colonization and of symptomatic infections with multidrug resistant (MDR) pathogens. Patients with catheters are often elderly, reside in a long-term care facility and have been widely exposed to multiple antibiotics.[12] This ultimately increases the risk of formation of biofilms with MDR pathogens. Although there have been many attempts to minimize the formation of these biofilms, including hydrophilic catheters, antibiotic-coated catheters and catheter irrigations, there has been mixed efficacy and the ISDA does not recommend their use.[23] In the event of a CAUTI, it is important to exchange the catheter quickly, as continuing treatment with the same catheter in place increases the risk of MDR colonization.[27] Recommendations remain to reduce the duration of catheterization with close attention to aseptic technique and good hand hygiene are critical to minimizing CAUTIs.[28]

Ureteral Dysfunction

Impaired ureteral function as seen in those patients with high intravesical pressure or vesicoureteral function predispose patients to upper UTIs. This is commonly seen in children with reflux and puts these patients at a high risk for renal scarring and recurrent UTIs. Antimicrobial prophylaxis has been found to reduce the risk of recurrent infection, but has not consistently been shown to reduce the risk of renal scarring.[29] Renal scarring in and of itself may put patients at additional risk for developing UTIs and thus mitigating the development of scarring is crucial to prevent future infections.

Impaired Host Response

One of the most challenging populations with cUTIs to manage are those who have impaired immune responses, including those with diabetes mellitus (DM), end-stage renal disease (ESRD), and solid organ transplantation, especially kidney transplant patients.[30] DM has an independent risk factor for UTIs in women.[31] There are no additional challenges in diagnosing patients with DM with UTIs, however clinicians should be vigilant about their timely diagnosis, as these patients rapidly progress to more severe illness as compared to the general population. In patients with diabetes, age above 60 years, chronic use of antibiotics, more than 6 physician contacts in the previous year, hospitalization in the previous year, and urinary incontinence were independently associated with severe UTIs.[32] Another study found that the higher morbidity associated with patients with DM and cUTIs were explained by the increased prevalence of cardiovascular morbidity and higher age.[33] In these patients, selection of empiric antibiotics and duration of treatment is the same as the general population. Of note, patients who are taking sodium/glucose co-transporter 2 (SGLT2) inhibitors for DM are at an increased risk of urinary tract infections as well as mycotic genital infections, likely due to increased glucose in the urine.[34]

Chronic kidney disease (CKD) has also been shown to place patients at higher risk for developing UTIs, likely due to the loss of antimicrobial properties in the urine, mild immunosuppression in anemia, and the inhibition of protective mucosal production in the urothelium.[30] This is most strongly correlated in patients with autosomal dominant polycystic kidney disease (ADPKD), where 21–75% of patients develop a UTI over their lifetime. These patients may develop pyonephrosis and pyocysts, where the cysts become infected, as this may exist without growth of urine cultures. In these specific patients, fluoroquinolones or TMP-SMX are recommended as they have better penetration for the cysts than standard antibiotics, such as beta-lactams and aminoglycosides. In addition, a population-based cohort study of nearly 80,000 patients with DM and CKD found that having higher frailty scores put patients at a higher risk of developing UTI, and that more severe frailty exhibited a trend of having higher rates of sepsis.[35]

Infections in kidney transplant recipients are associated with higher morbidity and mortality. There has been a significant reduction in mortality associated with UTI after kidney transplantation, now less than 5%.[30] UTIs, however, still account for about 40–50% of all infectious complications in these patients.[36] There has been mixed data on if age is independently associated with UTIs in this patient population, however the association of other comorbidities as patients age is likely thought to contribute to these infections. In addition, the type of immunosuppression has been shown to increase risk of UTIs. Azathioprine, mycophenolate mofetil, and anti-thymocyte globulin are all associated with higher rate of UTI, whereas other drugs such as calcineurin inhibitors and everolimus are not.[37] Many authors believe that infections are more likely to occur in the early post-transplant period, with reported rates of infection <30% in the first 3 months.[38,39]

Although now less fatal, acute pyelonephritis has been shown to be a risk factor for decline of renal function in renal transplant recipients,[40] thus rapid diagnosis and treatment is key to preserving graft function. In order to prevent this decline in graft function, many transplant centers screen for ASB and use antimicrobial prophylaxis in the first 6 months of transplant.[41] This long-term prophylaxis has been shown to reduce the risk of sepsis and bacteremia with TMP-SMX use, however there is no consensus on the regimen.[42,87,88] In an already vulnerable population, this prophylaxis can lead to antimicrobial resistance. Nearly 10% of patients are thought to be colonized pre-transplant with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE),[43] and this poses a challenge for treatment if patients then become septic in the intensive care unit post-transplant.

Pregnancy is one of the few clinical situations where ASB is treated, as untreated infections are associated with low birthweight and preterm delivery.[44] Antibiotic exposure in pregnancy can lead to both short and long-term complications, including congenital abnormalities, changes in gut microbiome and asthma, however only 10% of antibiotics have adequate data related to pregnancy.[45] Beta-lactams, vancomycin, nitrofurantoin, metronidazole and fosfomycin are generally considered safe, whereas fluoroquinolones and tetracyclines should be avoided.

Emerging Treatments
Fosfomycin
Although fosfomycin is indicated as a first-line therapy for treatment of uUTIs,[6] fosfomycin is not widely used for the treatment of cUTIs. Fosfomycin has extremely broad coverage against most uropathogens and is also active against extended-spectrum beta-lactamase (ESBL)/carbapenemase-producing enterobacteria, and bacteria resistant to quinolones.[46] Multiple studies have shown high rates of clinical cure for oral fosfomycin in patient with cUTIs[47] and MDR cUTIs.[48,49] There have also been promising studies comparing intravenous fosfomycin to piperacillin-tazobactam (PTZ) for acute pyelonephritis.[50] One limiting factor of fosfomycin use is the United States is cost, where fosfomycin has been documented as $67.49 per dose as compared to $0.52 per dose for nitrofurantoin and $0.06 per dose of TMP-SMX.[51] A recent cost analysis, however, shows that if taking into account local resistance, need for multiple courses of antibiotics and risk of progression to more serious effective, fosfomycin could be considered a cost-effective alternative to other treatments.[52] In Europe, fosfomycin is still more expensive than other first-line treatments, however this difference is much less pronounced and a cost-analysis found that when accounting for resistance rates, fosfomycin is the most cost-effective antibiotic.[53] As more manufacturers continue to make generic versions of fosfomycin, the cost will continue to decrease, making fosfomycin an increasingly viable alternative to current antibiotic regimens.

Intravesical Instillations
In a recent systematic review, aminoglycosides alone and aminoglycoside/polymyxin intravesical instillation has been shown to reduction of UTI and/or reduce the sensitivity of oral antibiotic therapy.[54] Many of the patients included in the reviewed studies were administering the instillation themselves, further reducing the need for hospitalization for treatment administration. Although the data provided is limited in long-term follow-up, there were no systemic side effects seen in intravesical instillation, such as ototoxicity and nephrotoxicity, that are usually seen with high-dose IV administration. Another systematic review included studies with gentamicin, neomycin/polymyxin, neomycin and colistin with similar results.[55] A 2017 retrospective study examined 22 patients with neurogenic bladder who performed clean intermittent catheterization who underwent prophylactic intravesical gentamicin irrigation.[56] These patients had fewer symptomatic UTIs and underwent fewer courses of oral antibiotics. In addition, the proportion of MDR organisms in urine cultures decreased and the rate of gentamicin resistance did not increase, with rare and mild adverse effects. Most studies, however, were only performed in a small cohort of patients and large-scale randomized controlled trials are still needed.[57]

Non-antibiotic instillations have also shown to be effective in preventing recurrent UTIs. A recent retrospective cohort study including 7 European institutions found that patients with recurrent UTIs who received 50mL hyaluronic acid and 2% chondroitin sulfate instillations had a decrease in the number of UTIs at 12 months and an increase in time between UTIs.[58] These non-antibiotic instillations are thought to restore the glycosaminoglycan layer in the bladder,

which is a key component of host defense. Although data is limited, both antibiotic and non-antibiotic intravesical instillations show promise in mitigating the impact of recurrent UTIs both on patients and on antibiotic resistance.

Clinical Trials for cUTIs

When treating cUTIs and pyelonephritis, source control and appropriate selection of antibiotics are key for treatment.[59] Generally, gram-negative pathogens are susceptible to new antimicrobials but there is limited treatment options for resistant enterococci.[1] Many new antibiotics are tested in patients with cUTI and acute pyelonephritis due to the high incidence and easy recruitment of participants. Because of the lack of consensus definition cUTI, there is variability in the inclusion criteria for the studies included in this review.[60] In addition, systemic symptoms, inflammatory markers such as C-reactive protein or procalcitonin, as well as detailed culture data make testing new antibiotics in cUTIs an ideal disease group. There have been many Phase 2 and 3 clinical trials for new antibiotics in the last few decades due to antibiotic resistance, but for the purposes of the review, we will focus on significant clinical trials from the last 5 years (Table 2). Much of the research is examining the effectiveness of new antibiotics against otherwise resistant pathogens, with great promise shown for those antibiotics that treat carbapenem-resistant infections.

Sitafloxacin versus Ertapenem

In 2017, a pilot study compared the use of oral sitafloxacin to ertapenem in patients with ESBL *E. coli* with non-bacteremic acute pyelonephritis.[61] Nineteen patients were enrolled in the sitafloxacin group with 17 in the ertapenem group. All patients were given 3 days of intravenous carbapenem and then switched for 7 days to either oral sitafloxacin or intravenous ertapenem. Baseline characteristics were similar between the two groups, except there was a lower proportion of previous urinary catheter insertion in the sitafloxacin group. At day 10, all but one patient in the ertapenem group had clinical cure and microbiological eradication was comparable between both groups, without significant side effects.

PTZ, Cefepime and Ertapenem

Seo et al conducted a prospective, randomized open-label study comparison of the therapeutic efficacy of PTZ, cefepime and ertapenem in patients with febrile nosocomial UTI with ESBL *E. coli*.[62] A total of 66 participants were evenly assigned to the PTZ and ertapenem group. Enrollment into the cefepime group was stopped after recruitment of 6 participants due to high failure rate, including 2 deaths. The clinical and microbiological response was 93.9% with PTZ and 97.0% with ertapenem, but the rates were not statistically different. Based on this study, patients with cUTI with ESBL-producing pathogens should not be treated with cefepime.

TANGO I: Meropenem-Vaborbactam versus PTZ

Kaye et al conducted a Phase 3 multicenter, multinational randomized clinical trial for patients with cUTI or acute pyelonephritis with 274 patients receiving meropenem-vaborbactam and 276 receiving PTZ.[63] After 15 total doses, patients could be transitioned to oral levofloxacin if met criteria for clinical improvement for 10 day total course. Primary endpoint for FDA criteria was overall success (clinical cure or improvement and microbial eradication composite) at end of intravenous treatment in the modified intent-to-treat (mITT) population. Primary endpoint for the EMA criteria was microbial eradication at test-of-cure (TOC) visit in the mITT and microbiologic evaluable populations. Superiority of meropenem-vaborbactam over PTZ was concluded for the overall success rate, at the lower limit of the 95% confidence interval.

PTZ versus Meropenem

This noninferiority randomized clinical trial in 391 patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance sought to determine if PTZ could be used as a carbapenem-sparing therapy.[64] Of these patients, 231 had infections from urinary tract source. Thirty-day mortality rate of patients treated with PTZ compared with meropenem was 12.3% and 3.7%, respectively, which did not meet the noninferiority margin and does not support the use of PTZ in these patients. Of note, mortality was higher in those with non-UTI infection source (12.8% vs 4.8%), however this was not statistically significant on multivariate analysis.

Table 2 Summary of Recent Clinical Trials for Antibiotics Treating Multidrug Resistant Organisms. Dosages Documented are for Those with Normal Renal Function and All Studies Adjusted Doses for Creatinine Clearance

Study	Participants	Antibiotics	Methods/Outcome	Results	Conclusions
Sitafloxacin vs carbapenem[61]	19 patients sitafloxacin group 17 patients carbapenem group Hospitalized patients with acute pyelonephritis with ≥10⁵CFU/mL ESBL *E. coli*	Given 3 days of IV carbapenems (meropenem 1g q8hr, imipenem 500mg q6hr, doripenem 500mg q8hr or ertapenem 1g qd), switched to either sitafloxacin (100mg BID) or the same carbapenem for 7 days	Clinical cure vs failure at day 10; microbiological response with sterile urine culture, persistent infection, or super infection	No significant difference; all but one in ertapenem group with clinical and microbiological cure	Proved non-inferiority of sitafloxacin
PTZ, cefepime and ertapenem[62]	66 patients with ESBL *E. coli* evenly split between 3 treatment groups	PTZ: 4.5mg q6hr IV Cefepime: 2g q12hr IV Ertapenem: 1g q24hr IV	10–14 days of assigned treatment, measured clinical and microbiological response	High failure rate in cefepime group with 2 deaths, no statistical significance between PTZ and ertapenem group	Cefepime should not be used for ESBL *E. coli*
Meropenem-vaborbactam vs PTZ[63]	274 meropenem-vaborbactam, 276 PTZ patients with cUTI or pyelonephritis	Meropenem-vaborbactam: 2g/2g over 3 hrs q8hr IV PTZ: 4g/0.5g over 30min q8hr IV	Phase 3 study, 15 total doses study drug, with transition to oral levofloxacin if clinically improved for 10-day total course	Superiority in mMITT and microbiological eradication of meropenem-vaborbactam compared to PTZ	FDA approval of meropenem-vaborbactam[89]
PTZ vs meropenem[64]	391 patients with *E. coli or Klebsiella* with ceftriaxone-resistance, 231 with urinary sources, randomized	PTZ 4.5g q6hrs IV Meropenem 1g q8hrs IV	Treatment for minimum 4 days up to maximum 14 days, measurement of 30-day all-cause mortality	30-day mortality of treatment was 12.3% with PTZ and 3.7% with meropenem, not statistically significant, worse mortality outcomes in non-UTI source	Should not use PTZ in ceftriaxone-resistant *E. coli* or *Klebsiella*
Cefiderocol vs imipenem[65]	452 patients, 2:1 cefiderocol vs imipenem-cilastatin, cUTI with carbapenem resistant pathogens	Cefiderocol: 2g q8hr IV Imipenem-cilastatin: 1g q8hr IV	Phase 2, noninferiority randomized control trial, treatment for 7–14 days	Clinical response 73% cefiderocol vs 55% imipenem-cilastatin group	Led to approval of cefiderocol by EMA and FDA[90]
Cefiderocol vs best-available therapy[66]	101 cefiderocol, 51 best available therapy in carbapenem resistant pathogens	Cefiderocol: 2g q8hr IV	Phase 3, open-label, descriptive phase 3 study	In cUTI, microbiological eradication 53% cefiderocol group and 20% in best available therapy group	
Eravacycline vs ertapenem[69]	1205 patients, 1:1 eravacycline or ertapenem for patients with cUTI	Eravacycline: 1.5mg/kg q24hr IV Ertapenem: 1g q24hr IV	5 days treatment drug with option to transition to oral regimen	Clinical and microbiologic response: 84.8%% and 94.9% (−10% CI: −14.1%, −6.0%),	Did not show non-inferiority, not approved for cUTI

Imipenem/ Relebactam vs Colistin[70]	31 patients, including PNA, cUTI, pyelonephritis or abdominal infections, 2:1 imipenem/relebactam or colistin for patients with imipenem resistant pathogens	Imipenem/relebactam: 500/250mg q6hr IV Imipenem 500mg q6hr IV Colistin: 300mg CBA loading dose, 150mg CBA maintenance dose IV	Phase 3, randomized, controlled, 5–21 days treatment	Clinical or microbiological response in UTI group: 72.7% imipenem/ relebactam and 100% colistin +imipenem, no statistical difference	Led to approval for cUTIs[71]
Plazomicin vs meropenem[72]	609 patients MDR (including carbapenem-resistant) *Enterobacteriaceae* cUTI, 1:1 randomized plazomicin vs meropenem	Plazomicin: 15mg/kg qd IV Meropenem: 1g q8hr IV	4 days study therapy with option for oral step-down for 7–10 day total treatment	At day 5, composite cure 88.0% plazomicin and 91.4% meropenem, non-inferiority.	Led to FDA approval for cUTI[73]
Cefepime/ Enmetazobactam vs PTZ[74]	345 cefepime/ enmetazobactam vs 333 PTZ for patients with cUTI or acute pyelonephritis from gram negative pathogens	Cefepime/enmetazobactam: 2/0.5g q8hr IV PTZ: 4/0.5g q8hr IV	Phase 3, randomized, double-blind, multicenter, 7–14 days treatment course	Combined cure in 79.1% cefepime/ enmetazobactam vs 58.9% PTZ, met noninferiority as well as superiority	Met Qualified Infectious Disease Product and Fast Track designation by FDA[75]
Tebipenem[76]	1372 patients, assigned 1:1 oral tebipenem vs IV ertapenem in patients with Enterobacterales bacteremia, including ESBL and fluoroquinolone resistant strains, with cUTI or acute pyelonephritis	Tebipenem pivoxil hydrobromide: 600mg q8hrs po Ertapenem: 1g q24hr IV	Phase 3, international, double-blind, received 7–10 days treatment	Overall response: 58.9% tebipenem vs 61.6% ertapenem, non-inferiority	Met criteria for non-inferiority, but did not receive FDA approval

Abbreviations: BID, twice daily; q, every; hr, hour; po, oral; CFU, colony-forming units; mL, milliliter; ESBL, extended-spectrum beta lactamase producing; *E. coli, Escherichia coli*; PTZ, piperacillin-tazobactam; mMITT, microbiological modified intent-to-treat; CBA, colistin base activity; IV, intravenous.

Cefiderocol

In this phase 2 multicenter, double-blind, parallel-group, noninferiority trial, 452 patients with cUTI with or without pyelonephritis were randomly assigned 2:1 to receive infusions of cefiderocol or imipenem-cilastatin.[65] The primary endpoint was a composite of clinical response and microbiological response at TOC for the mITT population. At TOC, clinical response was achieved by 73% of the cefiderocol group and 55% of patients in the imipenem-cilastatin group (p = 0.0004), establishing non-inferiority. Observed treatment differences were high for cefiderocol group, especially in those infected with resistant pathogens, thus clinical benefit for cefiderocol may be present.

A phase 3 open-label study was also conducted with patients admitted to the hospital with evidence of nosocomial pneumonia, blood stream infections, sepsis or cUTI and carbapenem-resistant gram-negative pathogen.[66] Participants were assigned 2:1 to either cefiderocol or best available therapy for 7–14 day treatment course. In patients with complicated UTI, primary endpoint was microbiological cure in mITT population, which was achieved in 53% of the cefiderocol group and 20% in best available therapy group, which proved similar clinical and microbiological efficacy. Both these trials led to the FDA and EMA approval of cefiderocol.[67]

IGNITE3: Eravacycline vs Ertapenem

Eravacycline is a tetracycline that has been approved for use in complicated intra-abdominal infections.[68] In a study of the use of eravacycline in cUTIs, Tetraphase Pharmaceuticals enrolled 1205 patients randomized 1:1 to receive either eravacycline or ertapenem for 5 days and then were eligible for transition to an oral agent.[69] Primary endpoints included both clinical and microbiological response. Responder rates in the mITT group were 84.8% and 94.8% for eravacycline and ertapenem, respectively (−10% CI: −14.1%, −6.0%), which did not show non-inferiority. Thus, eravacycline has not been approved for the use of cUTIs in the US.

RESTORE-IMI 1: Imipenem/Relebactam vs Colistin Plus Imipenem

Relebactam is a beta-lactamase inhibitor that can restore imipenem activity against imipenem non-susceptible pathogens.[70] In their phase 3 randomized, controlled, double-blind trial, hospitalized patients with hospital acquired or ventilator-associated pneumonia, complicated intraabdominal infection or cUTI caused by imipenem non-susceptible (but colistin and imipenem/relebactam susceptible) were randomized 2:1 to 5–21 days imipenem/relebactam or colistin +imipenem.[70] Sixteen patients had cUTI or pyelonephritis. Primary endpoint for patients with cUTI or pyelonephritis was a composite clinical and microbiological response at early follow-up, 5–9 days following end of therapy in mITT population. Overall response in the UTI group was observed in 72.7% imipenem/relebactam and 100% colistin+imipenem patients, with no statistical difference in overall response, day 28 favorable clinical response, 28-day mortality, or serious adverse events. This led to FDA approval for the treatment for cUTIs.[71]

Plazomicin vs Meropenem

In a multicenter, multinational, randomized, double-blind phase 3 trial, once-daily plazomicin was tested against meropenem for the treatment of cUTIs.[72] Plazomicin is an aminoglycoside with bactericidal activity against MDR (including carbapenem-resistant) Enterobacteriaceae. This noninferiority study randomly assigned 609 patients with cUTIs, including pyelonephritis, in a 1:1 ratio to receive plazomicin or meropenem with option for oral step-down therapy after receiving at least 4 days of study therapy for a total of 7 to 10 days of therapy. The primary endpoints were composite cure at day 5 and at the test-of-cure visit (15 to 19 days after initiation of therapy) in the mMITT population. At day 5, composite cure was 88.0% for plazomicin and 91.4% for meropenem, confirming noninferiority of plazomicin (95% CI −10.0 to 3.1). Superiority of plazomicin was exhibited at TOC visit, with composite cure of 81.7% for plazomicin and 70.1% meropenem (95% CI 2.7 to 20.3). This ultimately led to the approval of plazomicin for treatment of cUTI.[73]

Cefepime/Enmetazobactam vs PTZ

In a phase 3, randomized, double-blind, active-controlled, multicenter, noninferiority clinical trial, Kaye et al compared the efficacy of cefepime/enmetazobactam vs PTZ in patients with cUTI.[74] The primary outcome was combined clinical cure and microbiological eradication. After randomization, 79.1% (273/345) patients receiving cefepime/

enmetazobactam achieved combined cure as compared to 58.9% (196/333) receiving PTZ (between-group difference 21.2% [95% CI, 14.3% to 27.9%]). This met criteria for noninferiority as well as superiority for the primary outcome, which met criteria for Qualified Infectious Disease Product and Fast-Track Designation by the FDA.[75]

Tebipenem

Tebipenem pivoxil hydrobromide, an orally bioavailable carbapenem with activity against MDR Enterobacterales, was compared to intravenous ertapenem in a phase 3, international, double-blind, double-dummy trial.[76] A total of 1372 hospitalized patients were enrolled, in which 868 were included in the microbiologic intention-to-treat population. An overall response was seen in 58.9% of patients who received tebipenem pivoxil hydrobromide as compared with 61.6% who received ertapenem (95% CI −9.7 to 3.2). Clinical cure at TOC visit was observed in 93.1% of patients who received tebipenem pivoxil hydrobromide and 93.6% of patients who received ertapenem (CI −4.0 to 2.8). Although tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem, it did not meet the FDA criteria for noninferiority margin of −12.5%, and further studies are needed prior to approval.[77]

Recommendations

Global participation in both an antibiotic stewardship program and regulatory frameworks are necessary to mitigate the impact of antimicrobial resistance and promote the discovery of new drugs. In 2013, Rex et al proposed a regulatory framework with tiered approach based on the clinical need and data available.[78] The European Union (EU) launched New Drugs for Bad Bugs (ND4BB), a € 650 million program partnering industry, academia and biotech organizations to combat antimicrobial resistance in Europe.[79] The US also incentivized pharmaceutical companies to prioritize antibiotics by passing the Generating Antibiotic Incentives Now (GAIN) Act of 2011, which extended the exclusivity period for new infectious disease drug products by 5 years.[80] In 2016, the FDA announced the Limited Population Pathway for Antibacterial and Antifungal Drugs, which facilitated the approval of antimicrobial and antifungal drugs to treat serious and life-threatening infections in a limited population of patient with unmet needs.[81] In addition, the Joint Commission released a new and revised antibiotic stewardship program which outlined the current expectations for antibiotic stewardship nationwide.[67]

Improvements in diagnosing infections can also help meet the unmet needs for treating cUTIs. More rapid diagnostics can not only help provide more accurate care to patients in addition to reducing the risk of antibiotic resistance.[4] For example, a recent study found that in a model of point-of-care testing for *Neisseria gonorrhea* for strains that are not resistant to previous first-line therapies could reduce the total treatment time and reduce cost by using older more cost-effective antibiotics.[82] In addition, using older antibiotics could reduce resistance to newer, more expensive antibiotics and allow those to remain viable treatment options in the future. While urine culture remains the gold standard for diagnosing a UTI, PCR has been shown to be non-inferior to urine culture in patients with acute cystitis.[83] In their study, Wojno et al found that PCR exhibited greater accuracy than culture for pathogen detection and identification of bacteria in 36% with negative traditional culture. In addition, they found that PCR was much more sensitive in detecting polymicrobial infections than urine culture. To counter, however, PCR may be detecting bacteria that are not clinically significant, which may lead to increased use of antibiotics when not clinically indicated.

While bedside diagnostics are still in development, there have been validated tools to predict antibiotic resistance. Zilberberg et al developed a model assigning weighted points for the following characteristics: admission from an extended care facility (1), history of weight loss (1), early mechanical ventilation (1), age <50 years (2), male gender (3), catheter-associated UTI (4) or prior antibiotic treatment (4), and prior carbapenem-resistant infection (8). This tool had a high negative-predictive value. In patients who scored below 3, which accounted for approximately 30% of the cohort, there was a ~1% risk of cUTI caused by carbapenem-resistant organism. In addition, individualized multivariate predictive models used in combination with existing resistance-prediction models can predict the probability of suscept-ibility gram-negative bacteremia with the commonly prescribed antibiotics.[84] Patients who underwent intervention by applying these models to their care were more likely to have their therapy de-escalated. This study also found there was an increased proportion of patients who were on the narrowest adequate therapy at time of culture finalization. These tools can continue to be implemented until more rapid diagnostics are developed.

Conclusion

Complicated UTIs are an enormous burden on not only patients but also on the healthcare system. The lack of consensus definition has driven variability both in treatment options and in clinical trials. Special populations, especially those with catheters in place and those who have impaired immune response mechanisms make treating and diagnosing cUTIs a continued challenge. Antimicrobial resistance, especially in the context of treating cUTIs, continues to be one of the largest threats to our healthcare system globally. Regulatory frameworks in place have helped new drugs enter the pipeline for the treatment of resistant bacteria. Antibiotic stewardship programs will need to be prioritized moving forward to mitigate resistance in the future.

Abbreviations

UTI, urinary tract infection; uUTI, uncomplicated UTI; US, United States; cUTI, complicated UTI; ISDA, Infectious Disease Society of America; *E. coli, Escherichia coli*; TMP-SMX, trimethoprim-sulfamethoxazole; EAU, European Association of Urology; ESIU, European Association of Urology Section of Infections in Urology; FDA, Food and Drug Association; mL, milliliters; CFU, colony forming units; EMA, European Medicines Agency; AUA, American Urological Association; AMR, antimicrobial resistance; CAUTI, catheter-associated urinary tract infection; ASB, asymptomatic bacteriuria; CVA, costovertebral angle; MDR, multi-drug resistant; DM, diabetes mellitus; ESRD, end-stage renal disease; SGLT2, sodium/glucose co-transporter 2; CKD, chronic kidney disease; ADPKD, autosomal polycystic kidney disease; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; PTZ, piperacillin-tazobactam; PCR, polymerase chain reaction; mITT, modified intent-to-treat; TOC, test of cure.

Disclosure

The authors report no conflicts of interest in this work.

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