Epidemiology, definition and treatment of complicated urinary tract infections

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Abstract | UTIs are amongst the most frequent bacterial infections. However, the clinical phenotypes of UTI are heterogeneous and range from rather benign, uncomplicated infections to complicated UTIs (cUTIs), pyelonephritis and severe urosepsis. Stratification of patients with UTIs is, therefore, important. Several classification systems exist for the description and classification of UTIs, with the common rationale that cUTIs have a higher risk of recurrence or chronification, progression or severe outcome than uncomplicated UTIs. The pathophysiology and treatment of cUTIs and pyelonephritis are driven more by host factors than by pathogen attributes. cUTIs and pyelonephritis are associated with high antimicrobial resistance rates among causative pathogens. However, antimicrobial resistance rates can differ substantially, depending on the population being studied and whether the data being analysed are from surveillance studies, registry data or interventional studies, in which specific inclusion and exclusion criteria are used for patient selection. For example, antibiotic resistance rates are higher in patients with urosepsis than in those with less severe infections. Thus, treatment outcomes differ substantially among studies, ranging from 50% to almost 100% clearance of infection, depending on the patient population analysed, the UTI entities included and the primary outcome of the study. Pyelonephritis and cUTIs have emerged as infection models for the study of novel antibiotics, including extensive investigation of novel substances active against Gram-negative bacteria.

UTIs are amongst the most frequent bacterial infections in the community, as well as in health-care systems in general, and they are seen in many specialties, such as internal medicine, gynaecology, urology and intensive care medicine[1]. The clinical spectrum of UTI ranges from benign to life-threatening infections[2–5]. For decades, UTIs have therefore been classified into uncomplicated UTIs and complicated UTIs (cUTIs), with the aim of distinguishing infections with a benign course from those with a higher probability of recurrence or progression to severe infection. However, the classification systems employed by regulatory authorities, scientific societies or guideline groups are not unified and UTI classification is continuously evolving and developing[6]. Traditionally, uncomplicated UTIs referred to infections in non-pregnant, healthy women that resolve with antibiotic treatment, whereas all other UTIs were referred to as complicated, including cystitis in men. Some more recent definitions focus more on the relevance of complicating factors to cause a more complicated course of the infection and group healthy postmenopausal women or women with well-controlled diabetes mellitus amongst those with uncomplicated UTI. Infections can occur in any part of the urinary tract, including the urethra (urethritis), the bladder (cystitis), the ureters and the kidneys (pyelonephritis). Without treatment or in cases that are not resolved with antibiotics, in some patients with lower UTIs the infection can ascend and cause pyelonephritis or male genital infections, such as prostatitis or epididymo-orchitis, or can progress to severe, life-threatening urosepsis.

Incidence and prevalence rates vary substantially according to the UTI location, the medical specialist dealing with the patient, and patient sex and comorbidities, amongst others. Self-reported incidence rates for cystitis were 12.6% per year for women and 3.0% for men in the USA in the 2000 (REF.[7]). In 2000, hospitalization rates for pyelonephritis were 11.7 per 10,000 women and 2.4 per 10,000 men in the USA[8]. The Global Prevalence Study on Infections in Urology (GPIU) estimates that 1,866 of 19,756 (9.4%) urological patients hospitalized between 2005 and 2017 developed a cUTI during their hospital stay[9]. A wide variety of important medical aspects are intimately linked with UTIs, such as morbidity, mortality, long-term sequelae, antimicrobial administration and antimicrobial resistance, and costs. Morbidity rates for recurrent cystitis were assessed in the GESPRIT study[10], which reported a mean of

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Key points

- Complicated UTI (cUTI) is a heterogeneous entity comprising multiple forms.
- Classifications and definitions of cUTI have evolved over time and are sometimes very different.
- cUTI is a model infection for evaluating novel antibiotics that are active against Gram-negative bacteria and enterococci.
- The patients included and evaluated in different clinical trials and trial designs cannot be compared owing to different criteria employed.
- Standardization of definition and classification criteria for cUTIs are warranted.
- Evolution of trial designs might include criteria such as the emergence of antimicrobial resistance in various compartments, involving more patients with multidrug-resistant bacteria or superiority designs.

2.78 doctor visits, 3.09 sick leave days and 3.45 days of limited activity per year in women from Germany, Italy, Poland, Russia and Switzerland. In the COMBACTE-MAGNET RESCUING study, 30-day mortality was 15.2% for patients with catheter-associated UTI (CAUTI) and 6% for patients with a UTI not due to urinary catheters[11]. Although mortality in this study was high, it was not directly linked to the UTI but to the comorbidity of the patients[11]. In uncomplicated UTI, the causative bacterium is typically *Escherichia coli*[12]. However, in other UTI entities, such as health-care associated UTIs (HAUTIs), a wide variety of bacteria are causally implicated, including Gram-negative bacteria, such as Enterobacteriaceae other than *E. coli*, non-fermenting bacteria, such as *Pseudomonas* spp., and Gram-positive bacteria, such as enterococci or staphylococci[13] (FIG. 1). For this reason, and because antimicrobial resistance and multidrug resistance is high in HAUTIs[9], antibiotic treatment regimens differ substantially between cUTI entities.

UTIs have become a model for studying the pathophysiology of infections, such as host–pathogen interactions and evolutionary mechanisms of infection, and for developing novel antibiotics that are active against Gram-negative bacteria[12]. The experimental utility of UTIs is mainly because large quantities of causative pathogens can be isolated, the identity of the pathogen can be associated with the course of the disease, urine is an easily accessible primary diagnostic sample, and patients can be rapidly recruited for studies owing to the high prevalence of UTIs. However, novel antibiotics that are active against antibiotic-resistant enterococci are not frequently screened or tested in cUTIs or pyelonephritis, even though enterococci are the causative pathogen in at least 10% of cUTI cases and are an emerging and challenging nosocomial problem[13–15]. Although research in these different areas is highly dynamic and challenging, progress has been made in recent years. For example, virulence factors of uropathogenic bacteria and their functions in the host, as well as the mechanisms of invasion and colonization of urothelial cells, are being explored[12]. Our understanding of host–pathogen interaction pathways and the importance of the genetic background of the host for the development of asymptomatic and symptomatic disease is improving[16].

In summary, UTIs are common bacterial infections with considerable morbidity, which require antibiotic treatment and are, therefore, an important clinical setting for the emergence of antimicrobial resistance. In this Review, we describe the classification of the various clinical UTI entities and relate how our understanding of the pathogenesis of UTIs has evolved in recent years. Our focus is on cUTIs and pyelonephritis, for which the management is much more demanding than for uncomplicated UTIs. Most of the novel antimicrobial agents that are active against Gram-negative bacteria have been studied in cUTIs and/or pyelonephritis. Finally, we summarize phase II and III clinical trials performed in patients with cUTIs and/or pyelonephritis in the past 10 years.

Defining cUTI

The concept of uncomplicated UTI and cUTI was introduced in 1992 by the Infectious Diseases Society of America (IDSA) and by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) to obtain more homogeneous study groups when evaluating new anti-infective drugs in clinical trials[17,18].

In these classifications, patients with uncomplicated UTIs have no known risk factors that make them more susceptible to developing a UTI, a situation that is common in young, healthy women, whereas various risk factors are present in patients with a cUTI[17,18]. Some risk factors are related to the urinary tract, such as obstruction, urinary stones, diversion and catheterization, whereas others relate to kidney diseases or non-urogenital comorbidities, such as diabetes mellitus, malignancies or immune deficiency. Furthermore, if not properly treated, cUTIs have a higher risk of clinical complications than uncomplicated UTIs, for example, in pregnancy and childhood[17,18]. Risk sometimes also refers to an increased chance of disease recurrence. The classification also takes into account a different bacterial composition in the two disease entities. In uncomplicated UTI, *E. coli* is the major pathogen[19], whereas pathogens other than *E. coli* are common in cUTIs and consequently broad-spectrum antimicrobials and longer treatment duration have to be considered[20,21] (FIG. 1).

As the cUTI category encompasses such a wide range of manifestations, the disease is very heterogeneous, which has led to concerns that results of clinical studies of patients diagnosed with cUTI using one set of criteria might not be applicable to patients diagnosed using different criteria. For example, patients with kidney stones have a higher risk of UTI recurrence than patients without stones, because bacteria harboured

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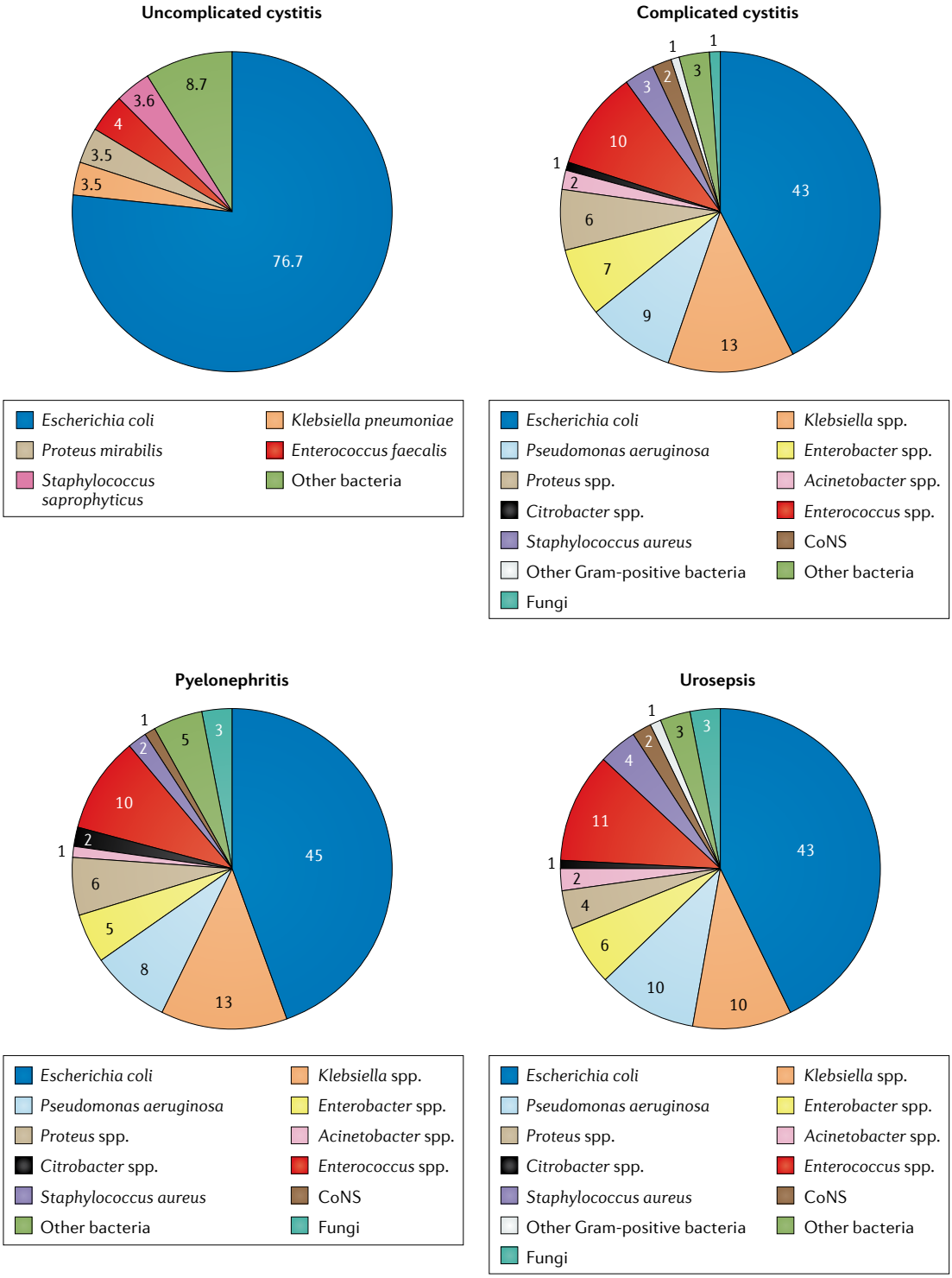

Fig. 1 | **Prevalence of uropathogenic bacterial species in various UTI entities.** The percentage of cases with the indicated taxa as the causative agent in different types of UTI, including uncomplicated cystitis[19] and different, complicated health-care-associated UTI entities[13] (namely, complicated cystitis, pyelonephritis and urosepsis). CoNS, coagulase-negative staphylococci.

in the stone mass may not be completely eradicated by antibiotic treatment[22]. The same is true for catheterized patients, as bacterial biofilms can form around urinary catheters[12]. The clinical investigations that are needed to diagnose risk factors or exclude them are also not clearly described[20].

In 2010, the European Section of Infections in Urology (ESIU) proposed an alternative definition and classification system for cUTI[20,21,23] that was based on GPIU surveillance data[9,24–26]. The main objective was to develop a classification that used the rational approach of other disease classifications, such as the

tumour–node–metastasis malignancy grading system that translates disease features in many tumours to a tripartite disease classification of low risk, intermediate risk and high risk, to guide clinicians in their daily work with patient assessment and treatment. New core features included the introduction of severity grading and categorization of risk factors rather than being based solely on risk factors as in the IDSA/ESCMID classification[27,28]. The severity grading is based on clinical presentation, and host risk factors are categorized in a system termed ORENUC (FIG. 2). This classification also considers pathogen risk factors, such as the identity and antibiotic susceptibility of the causative pathogen, as increasing antibiotic resistance reduces empiric treatment and cure rates. The availability of effective antibiotics is no longer only an issue in developing countries but is also becoming a problem in developed countries owing to increasing antibiotic resistance[14]. However, to date, antimicrobial resistance and antibiotic availability is not reflected in other classification systems. The ESIU classification is referred to by the Regulation and Quality Improvement Authority for Northern Ireland in their UTI guidelines for secondary care[29]. A combination of severity grade and phenotyping of risk factors is also used in Japanese guidelines[30] and by key opinion leaders in the USA in Uptodate[31].

Both the FDA and the EMA have defined cUTIs in their published guidance for testing antibacterial agents in cUTIs. The 2018 FDA guidance for industry in developing drugs for cUTI treatment[32] defines a cUTI as "a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms, including fever (i.e., oral or tympanic temperature greater than 38 degrees Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Patients with pyelonephritis, regardless of underlying abnormalities of the urinary tract, are considered a subset of patients with cUTIs"[32]. The FDA guidance also lists typical conditions that increase the risk of developing a cUTI: namely, an indwelling urinary catheter, ≥100 ml residual urine after voiding (neurogenic bladder), obstructive uropathy (from nephrolithiasis or fibrosis), azotaemia caused by intrinsic renal disease, and urinary retention (including that caused by benign prostatic hypertrophy).

The FDA guidance recommends that the primary efficacy outcome measure should be a responder outcome, namely clinical response (resolution of symptoms present at the start of the trial and no new symptoms) and microbiological response (reduction of bacterial pathogen in urine culture to $<10^3$ CFU/ml) criteria as co-primary end points[32].

The 2018 EMA guidelines on the evaluation of medicinal products indicated for the treatment of bacterial infections define patients with cUTI as having at least one complicating factor, such as an indwelling urethral catheter, urinary retention, urinary obstruction or neurogenic bladder[33]. In addition, EMA sets a threshold for the inclusion of patients with different cUTI entities in clinical trials, such that patients with acute pyelonephritis and those with cUTI should each comprise at least 30% of enrolled patients in studies that include both patients with acute pyelonephritis and those with a cUTI. The EMA also recommends including a combined clinical and microbiological success rate as co-primary end points.

Importantly, guidance from both regulatory bodies (FDA and EMA) focuses on a clinical and microbiological primary outcome, given the experience that culturable bacteria in urine samples and the presence of symptoms are not necessarily linked. For example, no bacteria can be cultured from urine samples in some patients with clinical signs of UTI, whereas patients with asymptomatic bacteriuria show no clinical signs of infection but substantial amounts of bacteria are present in their urine cultures.

cUTI and pyelonephritis are described and classified differently according to the different classification systems, which were originally developed to meet different aims. Some classification systems use a more extensive classification of uncomplicated UTI,

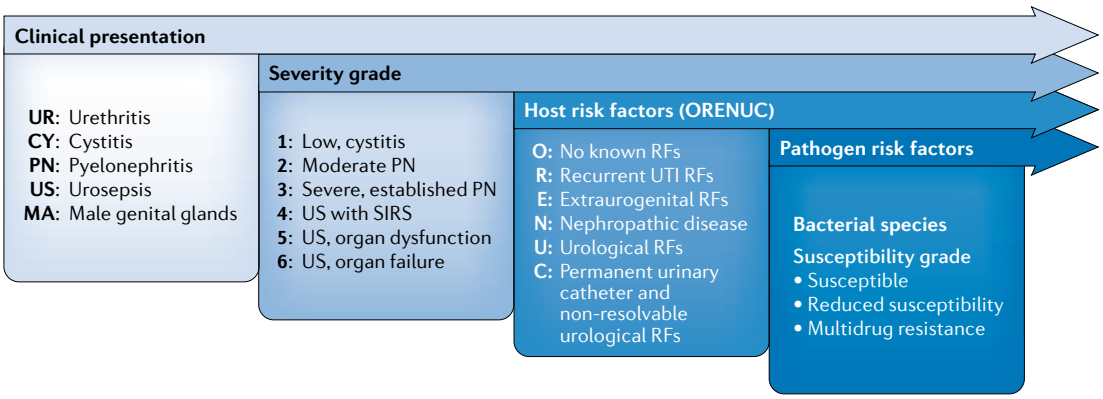

Fig. 2 | **The European Section of Infections in Urology classification of UTIs.** The classification and severity assessment[27] involves evaluation of the clinical presentations (that is, identifying the focus of infection), grading the severity of the infection (which is related to both location of the infection, symptom severity and severity of functional impairment), and identification of host and pathogen risk factors (RFs). SIRS, systemic inflammatory response syndrome. Reprinted with permission from REF.[27], European Association of Urology.

thereby decreasing the heterogeneity of cUTI, as some presentations are included in the uncomplicated UTI disease classification[34,35]. The classification systems of the scientific societies aim to describe all patient cases with cUTI in detail to guide clinical management accordingly[6,20,21,36], whereas regulatory body guidelines primarily work with case descriptions and aim to define homogeneous patient cohorts[32] to guide inclusion in clinical trials. However, these guidelines usually exclude a significant proportion of patients with cUTI, such as those with chronic indwelling catheters, renal insufficiency, immunosuppression or severe urosepsis. In our opinion, these comorbidities should be recognized and phenotyped, as in the ORENUC system (FIG. 2), as different patient cohorts with different complicating factors often differ by causative bacterial spectrum, antibiotic resistance and pathophysiological aspects[12].

Over the past 30 years, a number of changes have been made to classification systems, reflecting novel developments, such as the concept of asymptomatic bacteriuria. In the future, additional aspects and novel developments need to be evaluated for possible incorporation into classification systems. For example, molecular microbiological data might affect the definition of a UTI and the classification systems. Demonstration of causative pathogens and colony-forming unit (CFU) counts have been essential criteria since the original definition of HAUTIs by the CDC in 1988 (REFS[36,37]) for the purpose of defining and reporting these nosocomial infections. The importance of CFU counts in disease classification is currently challenged by detection of bacterial DNA using PCR and next-generation sequencing, although, to date, the requirement for CFU counts remains unchanged[38,39]. These counts are still a prerequisite for treatment with antibiotics, as opposed to molecular methods, which also detect remnants of dead microorganisms[40]. In addition, sometimes specimens other than urine might be more important, such as stone cultures, which have become an indicator of the risk of infective complications after treatment of urinary stones[22]. However, the use of alternative specimens has not yet been adopted by these classification systems.

All of these challenges strengthen the relevance of the ESIU classification of UTI for the definition of cUTI. The ESIU classification has several advantages, such as translating many different manifestations into a tripartite classification that can select for those patients who are at increased risk of treatment failure or recurrence and need special attention, such as interdisciplinary attendance (for example, diabetes control or nephrological assessment in cases of renal insufficiency), urological intervention (for example, stone disease and catheters), or broad-spectrum, last-resort antibiotic treatment (for example, in patients at risk of multidrug-resistant infections). For clinical studies, this classification is the only one that can separate the different cUTI entities. Currently, pyelonephritis is separated from lower UTI in regulatory studies, as, for example, a lower UTI complicated by bladder catheters, where the removal or exchange of the catheter in addition to antibiotic treatment might be sufficient, is markedly different from pyelonephritis complicated by stones, where decompression of the kidney might be necessary. In many clinical studies, patients with indwelling urinary catheters or persistent kidney stones are excluded because a higher failure rate is expected. However, only the ESIU classification system provides a detailed stratification according to different risk factors, severity and availability of effective treatment options. The patient cohorts in the different clinical trial databases differ substantially with regard to study design, bacterial spectrum, antibiotic resistance, severity of complicating factors and severity of the infection episode, so that the results from different studies cannot be compared. Adopting the ESIU system universally would make it possible to compare different studies and their included patient population. Thus, a classification system such as the ORENUC system is helpful for everyday clinical practice as well as for stratification in clinical studies[20,21]. For these reasons, we are convinced that the ESIU system is more detailed and comprehensive than other classification systems and should be adopted universally, including by regulatory bodies, such as the EMA and the FDA.

Pathophysiology of cUTIs

The severity of UTIs depends on a balance between the host defence mechanisms and the virulence of uropathogens (FIG. 3) but is only weakly predicted by the virulence factor profile of the infecting organism alone[41]. Bacterial pathogenesis is a combination of the ability of the bacterium to overcome the host defence mechanisms, form biofilms and survive in different milieus of the urinary tract or bloodstream.

Defence mechanisms

The host antibacterial defence in the lower urinary tract involves mechanical mechanisms, such as the physical flushing of pathogens from the urinary tract by urine flow, and mainly the innate immune system[16,42]. Attachment of bacteria to superficial bladder epithelial cells triggers an innate immune response mainly by signalling through Toll-like receptor 4 (TLR4), a member of the Toll/IL-1 receptor (TIR) domain super family[42]. These activated uroepithelial cells secrete cytokines and chemokines, such as IL-6, IL-8 and antimicrobial peptides[43]. IL-8 is a strong chemoattractant that binds to the IL-8 receptors CXC chemokine receptor type 1 (CXCR1) and CXCR2 on neutrophils, resulting in neutrophil recruitment and migration across the uroepithelium, where they clear uropathogens by phagocytosis[43]. Genetic polymorphisms that cause dysfunction of crucial receptors in the innate immune system might increase susceptibility to different forms of UTIs[16,44]. For example, polymorphisms in *TLR4* and *CXCR1* have been identified in patients with asymptomatic bacteriuria and acute pyelonephritis, respectively[16].

Pathogen virulence factors

The course of urinary microbial infections is also influenced by several pathogen-related factors, including bacterial motility, biofilm formation, presence of lipopolysaccharides, production of toxins and uptake

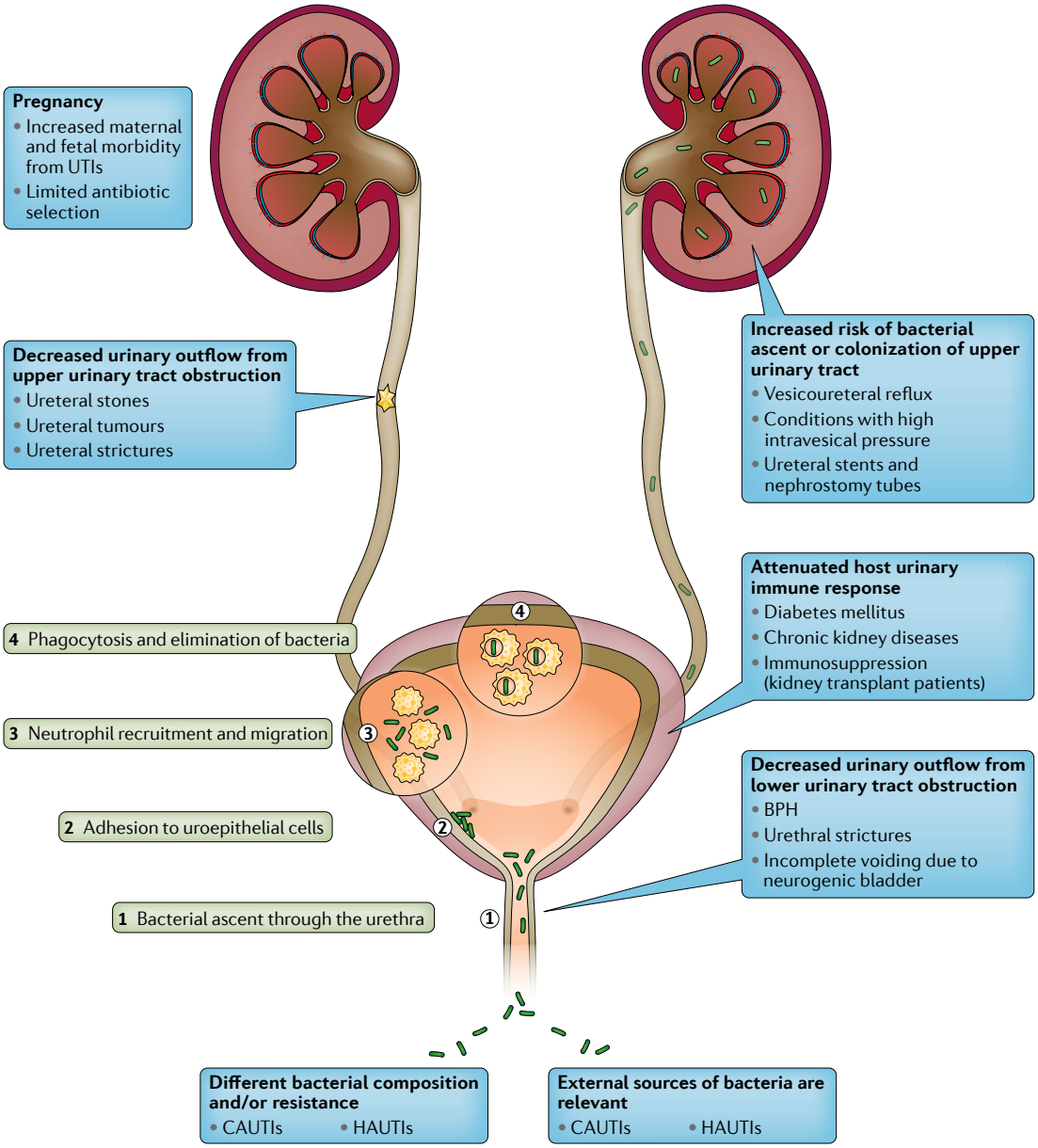

Fig. 3 | **Pathophysiological aspects of complicated UTI and pyelonephritis.** In healthy individuals, any bacteria that ascend the urethra and adhere to bladder epithelial cells activate Toll-like receptor signalling in these cells. This signalling induces secretion of cytokines and chemokines by these activated urothelial cells, which recruit neutrophils to clear the bacterial infection by phagocytosis. However, in complicated UTIs, various host factors can dampen the immune response or pathogen factors can alter the response of uropathogens to the immune system or antibiotic treatment, resulting in persistent infection. CAUTIs, catheter-associated UTIs; HAUTIs, health-care-associated UTIs.

of iron, which enhance microorganismal survival and thereby the potential of uropathogens to cause disease in a specific host environment[43]. The presence of virulence factors might be associated with disease severity and ascension to the upper urinary tract[45–48], as well as bacterial persistence[43].

Lipopolysaccharides are components of the outer membrane of Gram-negative bacteria, are strong inducers of host inflammation and are the major symptom mediator in Gram-negative septic shock[43]. Flagella-mediated bacterial motility can provide an advantage in competition for nutrients, thereby increasing bacterial virulence and enhancing bacterial dissemination to the upper urinary tract[45]. Effective iron uptake is necessary for bacteria to colonize the urinary tract. Iron acquisition systems, termed siderophores, such as aerobactin, scavenge iron from the environment to overcome iron limitation in the urinary tract, thus increasing bacterial virulence[12,49]. Bacterial toxins, such as haemolysin and cytotoxic necrotizing factor 1, increase virulence by directly damaging host tissues or by disabling the immune system[43]. Adhesins, such as type 1 fimbria, enable bacterial attachment in the bladder[12]. In a study comparing *E. coli* isolates from blood and urine in patients with urosepsis, among virulence loci only flagella, the adhesins type 1 fimbriae

and curli, the Fes/Fep iron acquisition system and the Cus heavy metal efflux system were associated with the bacteraemia phenotype[50].

Biofilms

Biofilm formation is an important virulence factor in cUTI and has been linked to specific risk factors, such as urinary catheters, stones and obstructive uropathy[51]. A biofilm is a structured community of microorganisms encapsulated within a self-developed polymeric matrix adherent to a surface[5].

The host–pathogen interactions in cUTIs differ from those in uncomplicated UTIs[12]. The host response can be dysfunctional in cUTIs. For example, bacterial biofilm production in cUTIs means that pathogens with reduced virulence, such as *Pseudomonas aeruginosa* or *Enterococcus faecalis*, can also cause severe infections[12,13]. cUTIs comprise many different clinical entities and, therefore, their exact pathophysiology can also be very different (FIG. 3).

Free outflow of urine is essential for the elimination of bacteria from the urinary tract. If bacteria are not mechanically cleared by normal urinary flow, then urinary stasis provides more time for bacterial adherence and multiplication[52]. Any anatomical or functional condition might lead to a breach of the mucosal protective layer, thereby facilitating bacterial invasion and activation of the host immune response[53]. Such conditions include urinary retention due to lower urinary tract obstruction, incomplete voiding due to neurogenic bladder disorders or upper urinary tract obstruction.

Foreign bodies in the urinary tract, most commonly indwelling urethral catheters, promote bacterial colonization by multiple mechanisms, an important one being biofilm formation. The presence of urethral catheters facilitates continuous access of bacteria to the urinary tract through ascent by an intraluminal or extraluminal route[54]. Pathogenic bacteria (FIG. 3) can originate from the patient's own gastrointestinal or perineal flora[55] but in the case of CAUTIs, exogenous sources contribute, such as cross-transmission from the hands of caregivers or health-care personnel[54,56,57]. In the case of long-term indwelling catheterization, colonization with multiple bacterial species is common[13,58] (FIG. 3), whereas in uncomplicated UTIs, single species, such as *E. coli* or *Staphylococcus saprophyticus*, are of aetiological relevance[12]. Long-term urinary catheterization inevitably leads to biofilm formation on the catheter surface[59], providing a favourable environment for bacterial persistence in the urinary tract. Biofilm development on catheters starts with deposition of urinary components and the formation of a conditioning film[60]. Host proteinaceous molecules in the film provide receptor sites for bacterial adhesins that facilitate uropathogen adherence[60,61]. Bacteria can sense proximity to surfaces, such as catheters, by detecting physicochemical changes in the surface microenvironment[61]. Once in close proximity to a surface, an active process of adhesion involving reversible hydrophobic and electrostatic forces occurs and is followed by irreversible bacterial attachment mediated by bacterial polysaccharides[60]. The molecules involved in biofilm formation differ from species to species, such as the (p)ppGpp–CodY network in *E. faecalis*[62] and the elastase LasB or the exopolysaccharide alginate in *P. aeruginosa*[63]. Organisms within the biofilm are protected from the host defence mechanisms, including flushing by urine flow[60]. Most antibiotics do not effectively treat bacteria in biofilms, as sessile bacteria can activate genes that alter the cell envelope or molecular targets of antibiotics[64]. In addition, sessile bacteria grow more slowly than planktonic bacteria and might therefore evade antibiotics that are effective against dividing bacteria[60,65].

Pathogenesis in special risk groups

The risk of developing a cUTI is increased in various patient populations, typically as a result of reduced clearance of uropathogens or increased bacterial colonization of the urinary tract.

Ureteral dysfunction. Conditions with high intravesical pressure or vesicoureteral reflux facilitate the ascent of bacteria to the ureter or the renal pelvis and increase the risk of upper UTIs, as is frequently observed in children with reflux[66]. Recurrent pyelonephritis secondary to vesicoureteral reflux can lead to renal scarring, which can adversely affect renal growth and result in long-term damage to the kidney parenchyma, with bilateral scarring increasing the risk of renal insufficiency[66,67]. Furthermore, a dysfunctional CXCR1 might lead to a dysfunctional neutrophil response and, therefore, drives susceptibility to pyelonephritis and renal scarring[68,69].

Impaired host response. In immunocompromised patients, local or systemic host defence mechanisms can be attenuated, and UTIs can present with atypical clinical manifestations in which the classical symptoms are absent[4] (TABLE 1). In patients with diabetes mellitus, increased risk of UTIs is considered to be associated with impaired local host defence mechanisms, especially in uncontrolled diabetes. Glucosuria, defects in neutrophil function and an increased bacterial adherence to uroepithelial cells are suggested mechanisms for an impaired local host defence[70]. In addition, bladder dysfunction associated with diabetic neuropathy worsens the situation in patients in whom the UTI is uncontrolled and prolonged. Chronic kidney disease is associated with a decreased efficacy of anti-infective therapy[71]. The proposed mechanisms for this treatment failure include decreased local host response associated with loss of antibacterial properties in the urine[72], immunosuppression in uraemia[73–75], inhibition of the production of urothelial antimicrobial substances[73–75] and lower antimicrobial levels in the kidneys owing to decreased antibiotic diffusion into low-functioning kidney units[76,77].

Kidney transplantation. UTIs are associated with higher morbidity and mortality in kidney transplant patients[4]. Historically, the mortality of infectious complications in the first year after renal transplantation was approaching 50%. With the continuous advance in surgical techniques and post-transplantation care, the 1-year mortality due to infectious complications has decreased to less than 5%[78]. Furthermore, acute pyelonephritis of

Table 1 | **Classical symptoms of different UTI entities**

Acronym	Clinical diagnosis	Clinical symptoms	Severity grade
CY-1	Cystitis	Dysuria, frequency, urgency, suprapubic pain; sometimes unspecific symptoms	1
PN-2	Mild to moderate pyelonephritis	Fever, flank pain[a], CVA tenderness[a]; sometimes unspecific symptoms with or without symptoms of cystitis	2
PN-3	Severe pyelonephritis	As for PN-2, but, in addition, nausea and vomiting with or without symptoms of cystitis	3
US-4[b]	SIRS	Temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg (<4.3 kPa), WBCs >12,000 cells/mm^3 or <4,000 cells/mm^3 or ≤10% immature (band) forms with or without symptoms of cystitis or pyelonephritis (>2 SIRS criteria must be met for US-4 diagnosis)	4
US-5[b]	Severe urosepsis	As for US-4, as well as organ dysfunction, hypoperfusion or hypotension; hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute change in mental status	5
US-6[b]	Uroseptic shock	As for US-4 or US-5, as well as hypotension despite adequate fluid resuscitation and the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute change in mental status; patients who are on inotropic or vasopressor agents may not be hypotensive when perfusion abnormalities are measured	6

CVA, costovertebral angle; SIRS, systemic inflammatory response syndrome; WBCs, white blood cells. [a]Not seen in transplant patients; instead graft pain may be seen in some cases. [b]Sepsis definitions have recently been refined and the current definitions will be reconsidered once the new definitions have been validated. Reprinted with permission from REF.[4], Elsevier.

the transplanted kidney was shown to be an independent risk factor for decline of renal function[79]. The effect of UTIs and acute pyelonephritis on graft function was evaluated in 177 kidney transplant recipients. In this patient group, the cumulative incidence of UTIs was 75.1% and that of acute pyelonephritis was 18.7%. UTIs occurred mainly during the first year after transplantation and *E. coli*, *P. aeruginosa* and *Enterococcus* spp. were the most common uropathogens. The risk of developing acute pyelonephritis was 64% higher in female than in male recipients and was correlated with the frequency of recurrent UTIs ($P < 0.0001$) and rejection episodes ($P = 0.0003$). Acute pyelonephritis did not alter graft or recipient survival, although compared with patients with uncomplicated UTIs, patients with acute pyelonephritis exhibited both a significant increase in serum creatinine and a decrease in creatinine clearance, which was already detected after 1 year (abbreviated Modification of Diet in Renal Disease measurement of glomerular filtration rate 39.5 ± 12.5 ml/min/1.73 m^2 or 54.6 ± 21.7 ml/min/1.73 m^2 in patients with acute pyelonephritis or uncomplicated UTI, respectively; $P < 0.01$), which persisted 4 years after transplantation (at ~50% of 1-year levels). Multivariate analysis revealed that acute pyelonephritis represents an independent risk factor associated with the decline of renal function ($P = 0.034$). Risk factors for post-transplantation UTIs include age[80,81], female sex in adults[81,82], long pre-transplantation dialysis time[80] and urinary tract obstruction[82].

Pregnancy. Untreated asymptomatic bacteriuria and upper UTIs in pregnant women are associated with low birthweight and preterm delivery[43,83,84]. A meta-analysis of eight randomized controlled trials with 1,689 women receiving antibiotic treatment for asymptomatic bacteriuria showed a reduction in the incidence of pyelonephritis and a reduction in the risk of low birthweight (relative risk (RR) = 0.58, 95% confidence interval (CI) 0.36–0.94) and data from four different randomized controlled trials with 854 women in this meta-analysis showed a reduced risk of preterm delivery if asymptomatic bacteriuria was treated with antibiotics (RR = 0.34, 95% CI 0.18–0.66)[84], although one study did not find an association between untreated asymptomatic bacteriuria and preterm delivery[85]. This effect might be mediated by lipopolysaccharides, which in animal models have been proposed as initiators of preterm labour, although in humans the exact pathophysiology is not completely understood[86]. The choice of antimicrobial agents and duration of treatment in pregnant women is further limited by possible adverse effects, both short-term (for example, congenital abnormalities) and long-term (for example, changes in the gut microbiota, asthma and atopic dermatitis), in the newborn[87].

Antibiotic resistance in cUTI and pyelonephritis

Antibiotic resistance is common in UTIs and is increasing[9,88]. The resistance rates differ substantially depending on geographical region and the types of studies, ranging from registry studies to specific surveillance studies to interventional studies[9,14,24–26,88]. In a summary of worldwide antibiotic resistance in Gram-negative uropathogens, obtained from studies published between 2009 and 2014, from 10 to 80% of pathogens were resistant to fluoroquinolones, 10 to 70% to third-generation cephalosporines and 5 to 35% to carbapenems, depending on the geographical location[88].

The GPIU evaluated antimicrobial resistance exclusively in urological inpatients with HAUTIs[25,26,89]. In the initial report for the period from 2003 to 2010, amongst 1,866 patients with a HAUTI, the causative bacteria included *E. coli* (39%), *Klebsiella* spp. (11%), *Proteus* spp.

(5.7%), *Enterobacter* spp. (5.3%), *P. aeruginosa* (10.8%), *Enterococcus* spp. (11.5%) and *Staphylococcus aureus* (3.1%)[9]. A follow-up study included data for resistance rates for all bacterial species to individual antibiotics and antibiotic combinations from 2003 to 2017 (REF.[89]) (TABLE 2). In a sub-analysis of patients with reported urosepsis in this study, antimicrobial resistance rates were even higher than in UTI without sepsis, for example, resistance to ceftazidime and levofloxacin was 46% and 58%, respectively, in patients with urosepsis ($P = 0.008$) and was 33% and 39%, respectively, in patients with non-septic pyelonephritis ($P = 0.009$)[13].

These data show that antimicrobial resistance is especially prominent in Gram-negative uropathogens and enterococci. Antimicrobial resistance varies widely by geographical location and clinical conditions. Higher resistance rates are generally associated with specific risk factors, such as age and comorbidity, which need to be taken into account for prognosis and treatment. Such variability makes it impossible to give exact treatment recommendations on a global level; thus, each medical facility needs to run its own resistance surveillance programme to ensure optimal empirical treatment regimens.

Table 2 | **Antimicrobial resistance rates for various HAUTI entities in Europe**

Antimicrobial agent or combination	Percentage resistance rate (*n*)			
	Cystitis	Pyelonephritis	Urosepsis	Overall
Amoxicillin	60.4 (397)	64.2 (321)	63.8 (296)	63.4 (1,014)
Aminopenicillin–β-lactamase inhibitor[a]	43.8 (331)	52.1 (261)	60.4 (230)	51.1 (822)
Piperacillin–tazobactam	25.0 (252)	27.4 (201)	34.6 (179)	28.5 (632)
Cefuroxime	38.0 (342)	42.5 (275)	57.2 (187)	44.0 (804)
Cefotaxime	29.2 (318)	33.8 (275)	54.1 (194)	36.9 (787)
Ceftazidime	27.5 (287)	27.7 (252)	44.0 (161)	31.4 (700)
Ciprofloxacin	41.9 (393)	44.3 (318)	58.4 (255)	47.1 (966)
Levofloxacin	40.5 (254)	37.4 (195)	59.3 (123)	43.5 (572)
Sulfamethoxazole–trimethoprim	48.1 (339)	44.2 (267)	53.9 (228)	48.4 (834)
Gentamicin	32.4 (379)	31.6 (319)	36.9 (265)	33.4 (963)
Imipenem	6.7 (282)	10.0 (238)	8.2 (195)	33.4 (715)
Amoxicillin plus gentamicin	23.9 (318)	22.3 (255)	28.5 (203)	24.6 (776)
Aminopenicillin–β-lactamase inhibitor[a] plus gentamicin	21.0 (276)	21.3 (211)	30.1 (159)	23.4 (646)
Ceftazidime plus ciprofloxacin	21.2 (259)	21.1 (228)	41.0 (144)	25.7 (631)
Ceftazidime plus gentamicin	17.5 (251)	15.5 (220)	29.7 (228)	19.4 (599)
Ceftazidime plus sulfamethoxazole–trimethoprim	17.8 (219)	21.9 (178)	32.7 (101)	22.3 (498)
Piperacillin–tazobactam plus ciprofloxacin	19.3 (228)	18.8 (181)	33.1 (145)	22.7 (554)
Piperacillin–tazobactam plus gentamicin	15.6 (225)	14.1 (170)	20.3 (128)	16.3 (523)
Piperacillin–tazobactam plus sulfamethoxazole–trimethoprim	15.0 (194)	16.1 (137)	22.2 (99)	17.0 (430)
Ciprofloxacin plus gentamicin	27.7 (332)	26.5 (264)	33.7 (193)	28.8 (789)
Ciprofloxacin plus sulfamethoxazole–trimethoprim	29.1 (289)	31.0 (210)	40.1 (157)	32.3 (656)

Data are for the years 2004 to 2017 and are adapted from the GPIU study[89].
HAUTI, health-care-associated UTI. [a]Average for all combinations of these agents.

Phase II and III trials in cUTIs

Source control and the choice of appropriate antibiotics are essential in the treatment of cUTI and pyelonephritis[3]. Source control includes decompression of an obstructed upper or lower urinary tract by internal or external splints or catheters and the drainage of abscesses[3]. In addition, other complicating factors, such as uncontrolled diabetes mellitus, should be medically managed[90]. The published resistance rates from phase II and III clinical trials in patients with cUTIs or pyelonephritis described below are difficult to compare, as the patient populations included in these trials and the pathogens causing the infections can differ substantially according to the different criteria for participant inclusion and exclusion.

Almost all novel antibiotics that are effective against Gram-negative pathogens, but for unknown reasons not those against antibiotic-resistant enterococci, have been tested in clinical trials in patients with cUTIs or pyelonephritis. Novel antibiotics are tested in patients with cUTIs or pyelonephritis because these are very common infections, thereby guaranteeing rapid recruitment of patients. The bacterial spectrum of these novel antibiotics is generally very broad and covers the majority of clinically important Gram-negative pathogens (FIG. 1), including multidrug-resistant organisms, often with different resistance mechanisms. Consequently, phase II and III clinical trials in patients with cUTIs or pyelonephritis deliver extensive data on different uropathogens. An additional advantage of these studies in cUTI or pyelonephritis is that diagnosis is precise and objective owing to the presence of typical symptoms indicating infection of the lower and/or upper urinary tract, and the presence of a typical uropathogen, in conjunction with local and/or systemic inflammatory signs and signals, such as leukocytes, C-reactive protein or procalcitonin. Furthermore, the course of the infection can be easily monitored longitudinally by measuring symptoms, inflammatory signs and bacteria in the urine. The longitudinal monitoring can, in most cases, establish an association between symptoms and treatment outcome; thus, eradication of bacteria and improvement of symptoms are indicative of a cure or, conversely, bacterial persistence and no improvement or worsening of symptoms are indicative of treatment failure. This cause–effect relationship is more difficult to study in other indications; for example, in intra-abdominal infections, in which no follow-up microbiology culture is available because the abdominal focus of infection is not as easily accessible as in UTIs. In addition, surgical control of the focus of infection in abdominal infections might be much more important for curing the patient than antibiotic treatment. Furthermore, in lung infections, the typical causative pathogen is often more difficult to detect than in UTI, as mixed infections are more frequent and

Box 1 | **Definitions of patient populations in clinical trials in complicated UTIs**

Intent-to-treat (ITT)
The population of patients who are randomly assigned to any study arm.

Modified intent-to-treat (MITT)
The population of patients who are randomly assigned to receive any amount of study drug.

Microbiological modified intent-to-treat (mMITT)
The subset of patients in the MITT population who have at least one acceptable causative uropathogen in a study-qualifying pretreatment baseline urine specimen or a blood culture.

Microbiologically evaluable (ME) at test of cure (TOC)
The subset of patients in the mMITT population who adhere to study procedures and have an interpretable urine culture at the TOC visit.

Clinically evaluable (CE) at TOC
The subset of patients in the mMITT population who adhere to study procedures and have a clinical outcome at the TOC visit. An interpretable urine culture at the TOC visit is not required.

ME at late follow-up (LFU)
The subset of patients in the ME at TOC population who are microbiological cures at the TOC visit, adhere to study procedures and have an LFU assessment or were classified as a microbiological failure prior to the LFU visit.

CE at LFU
The subset of patients in the CE at TOC population who are clinical cures at the TOC visit, adhere to study procedures and have an LFU assessment or are classified as a clinical failure prior to the LFU visit.

Safety population
All patients who received any amount of the study drug[32].

follow-up cultures are more difficult to obtain than in urine from patients with a UTI. Consequently, conducting clinical trials in patients with cUTI or pyelonephritis can produce a substantial amount of pharmacokinetic and pharmacodynamic data that can be leveraged for use in other infection types.

Owing to these aspects, cUTI and pyelonephritis have become model indications for pharmaceutical companies to study novel anti-infective substances, not only to obtain regulatory approval for treatment of these indications with the novel drug but also to obtain important information about its anti-infective behaviour. In interventional clinical trials in cUTI or pyelonephritis, various definitions of patient populations, based on the treatment administered and the outcome at specific points of the study (BOX 1), are usually applied, although not all populations are investigated in all studies.

Various phase II and III interventional studies have been performed in cUTI and/or pyelonephritis in the past decade[91], encompassing different inclusion and exclusion criteria, study designs, different clinical end points, clinical distinctions in patients and infections classified according to the ORENUC criteria, thereby highlighting commonalities and differences in these studies (Supplementary Table 1 provides an overview of studies published in the last 20 years).

Piperacillin versus imipenem

In a 2002 phase III study[92], monotherapy with piperacillin–tazobactam (2 g/0.5 g 8-hourly) was compared with imipenem and the imipenem metabolism inhibitor cilastatin (0.5 g each 8-hourly) for 5–14 days in 337 patients with acute pyelonephritis or cUTI. Hospital inpatients were included if they had typical cUTI symptoms, such as dysuria, frequent micturition, flank pain, pyuria and bacteriuria. The CFU eligibility criterion varied depending on the type of urine specimen and sex of the patient. cUTIs were defined by the presence of complicating factors, such as anatomical or functional abnormalities, neurogenic bladder disturbance, urological intervention or various types of urinary catheter. The microbiological success rate and the clinical success rate at early follow-up were separate primary study end points, not co-primary end points. Clinical success rate was evaluated in the intent-to-treat (ITT) population and microbiological success rates in the modified intent-to-treat (MITT) population. Piperacillin–tazobactam was non-inferior to imipenem–cilastatin in both clinical and microbiological response rates (83.0% versus 79.9% at early follow-up in the ITT population and 57.8% versus 48.6% in the MITT group, respectively).

Levofloxacin versus doripenem

In another phase III study published in 2009, low-dose levofloxacin (250 mg 24-hourly) was compared with doripenem (500 mg 8-hourly) in 753 patients with cUTI or pyelonephritis[93]. Treatment duration was 10–14 days, with the option of levofloxacin oral step-down therapy after 3 days of intravenous therapy. Patients were included if they had symptoms of upper or lower UTI and bacteriuria with $\geq 10^5$ CFU/ml. The primary study end point was microbiological cure rate in the microbiologically evaluable (ME) at test-of-cure (TOC) visit group. The co-primary end point was the microbiological cure rate in the microbiologically MITT (mMITT) population. The microbiological cure rate was 82.1% for doripenem and 83.4% for levofloxacin in the ME at TOC group (545 patients) and 79.2% for doripenem and 78.2% for levofloxacin in the mMITT cohort (648 patients), confirming the non-inferiority of levofloxacin in the two populations. Clinical cure rates were 95.1% with doripenem and 90.2% with levofloxacin at the TOC visit.

ASPECT

The 2015 phase III ASPECT cUTI study compared ceftolozane–tazobactam (1.5 g 8-hourly) with high-dose levofloxacin (750 mg 24-hourly) in 1,083 patients with cUTI or pyelonephritis[94]. Treatment duration was 7 days with no oral step-down. Hospitalized inpatients were included if they had typical cUTI symptoms, pyuria and bacteriuria with $\geq 10^5$ CFU/ml. The co-primary end points were microbiological eradication and clinical cure 5–9 days after treatment in the mMITT population. Composite cure rates in the mMITT population were 76.9% with ceftolozane–tazobactam and 68.4% with levofloxacin, thus confirming the superiority of ceftolozane–tazobactam over levofloxacin for all patients.

RECAPTURE

The phase III RECAPTURE study compared ceftazidime–avibactam (2.5 g 8-hourly) with doripenem (500 mg 8-hourly) in 1,033 patients with cUTI or

pyelonephritis[95]. Treatment duration was 10–14 days, with the option of ciprofloxacin or trimethoprim–sulfamethoxazole oral step-down therapy after 5 days of intravenous therapy. Hospitalized patients were included if they had typical cUTI symptoms, pyuria and bacteriuria with ≥10^5 CFU/ml Gram-negative uropathogens. The co-primary end points for FDA were the proportion of patients with symptomatic resolution of UTI-specific symptoms (clinical cure) at day 5, and the proportion of patients with both microbiological eradication and symptomatic resolution of UTI-specific symptoms at TOC visit in the mMITT population. Clinical cure rates were 70.2% for ceftazidime–avibactam and 66.2% for doripenem at day 5, thus confirming non-inferiority of ceftazidime–avibactam; combined symptomatic resolution and microbiological eradication at the TOC visit were 71.2% for ceftazidime–avibactam and 64.5% for doripenem, thus demonstrating the superiority of ceftazidime–avibactam.

REPRISE

The phase III REPRISE study compared ceftazidime–avibactam (2.5 g 8-hourly) with the best available treatment in 306 patients with cUTI or pyelonephritis or 27 patients with complicated intra-abdominal infections caused by ceftazidime-resistant pathogens[96]. Treatment duration was 5–21 days. The primary end point was clinical response at TOC visit (7–10 days after last infusion of study therapy) in the mMITT population. Clinical cure rates in the cUTI group were similar in the two groups, with 92% for ceftazidime–avibactam and 94% for best available therapy (usually a carbapenem).

Sitafloxacin versus ertapenem

A 2017 pilot study evaluated an oral switch therapy in 36 patients with pyelonephritis due to *E. coli* that produce extended spectrum β-lactamase (ESBL)[97]. All patients received carbapenem intravenously for 3 days and were then switched to either 7 days of oral sitafloxacin (100 mg 12-hourly) or intravenous ertapenem (1 g 24-hourly). Primary outcome was clinical cure at day 10 in the ITT population. The clinical cure rates were 100% with sitafloxacin and 94.1% with ertapenem, showing comparable results in the two groups. Of the ESBL-producing *E. coli* isolates, 94.4% were susceptible to sitafloxacin.

Piperacillin, cefepime and ertapenem

A randomized, open-label study compared piperacillin–tazobactam (4.5 g 6-hourly), cefepime (2 g 12-hourly) and ertapenem (1 g 24-hourly) in 72 patients with HAUTIs due to ESBL-producing *E. coli*, including those patients with septic shock[98]. Treatment duration was 10–14 days, and primary outcomes were not prespecified. Clinical cure rate was 93.9% with piperacillin–tazobactam and 97% with ertapenem, and the difference was not statistically significant ($P = 0.5$). After recruitment of 6 patients in the cefepime group, assignment to cefepime was stopped owing to treatment failure rate in 4 of 6 patients, including 2 deaths. Therefore, from this study it is not evident that cefepime could be used in patients with cUTI because of ESBL-producing pathogens.

Dose-ranging study of relebactam

A phase II study compared imipenem–relebactam (625 mg 6-hourly), imipenem–relebactam (750 mg 6-hourly) and imipenem alone (500 mg 6-hourly) in 302 patients with cUTI or pyelonephritis[99]. Treatment duration was up to 14 days, and oral step-down to ciprofloxacin was possible after 4 days of intravenous treatment. The primary efficacy end point was the proportion of patients with a favourable reduction in CFU count, which was defined as microbiological response at discontinuation of intravenous therapy in the ME population. Microbiological response rates were 95.5% for 750 mg imipenem–relebactam, 98.6% for 625 mg imipenem–relebactam and 98.7% for imipenem alone, confirming the non-inferiority of imipenem monotherapy.

TANGO I

The phase III TANGO I study compared meropenem–vaborbactam (4 g 8-hourly) with piperacillin–tazobactam (4.5 g 8-hourly) in 585 patients with cUTI or pyelonephritis[100]. Treatment duration was 10 days, and after 5 days an oral step-down treatment to levofloxacin (500 mg 24-hourly) was possible. The FDA primary outcome was a composite outcome of clinical cure and microbial eradication (<10^4 CFU/ml urine) at the end of the intravenous treatment for the mMITT population. The overall success rate in the mMITT population was 98.4% with meropenem–vaborbactam versus 94.0% with piperacillin–tazobactam, demonstrating superiority of meropenem–vaborbactam (95% CI 0.7–9.1, $P < 0.001$ for non-inferiority). If non-inferiority was demonstrated in FDA or EMA primary end points, the study protocol and statistical analysis plan included an assessment of superiority using the CI to determine whether the lower bound of the two-sided 95% CI was greater than 0. According to the prespecified statistical plan, superiority of meropenem–vaborbactam over piperacillin–tazobactam was concluded for the overall success rate, as the lower limit of the 95% CI (0.7%) exceeded 0 ($P = 0.01$).

MERINO

An open-label, randomized study compared piperacillin–tazobactam (4.5 g 6-hourly) with meropenem (1 g 8-hourly) in 391 randomized patients with bloodstream infections with ceftriaxone-resistant *E. coli* or *K. pneumoniae*, including 231 patients with a urinary tract source[101]. Treatment duration was 4–14 days. The primary efficacy outcome was all-cause mortality at 30 days after randomization in the MITT population. Mortality was 12.3% with piperacillin–tazobactam versus 3.7% with meropenem and did not meet non-inferiority criteria. Mortality was substantially higher in patients with a non-UTI infection source (12.8%) than in patients with a UTI infection source (4.8%). Multivariate analysis confirmed that group randomization was balanced and not influenced by the infection source.

APEKS-cUTI

A phase II study compared cefiderocol (2 g 8-hourly) with imipenem–cilastatin (1 g 8-hourly) in 495 patients with cUTI or pyelonephritis[102,103]. Treatment duration was 7–14 days. The primary efficacy end point was

the composite of clinical response and microbiological response at the TOC visit for the mMITT population. Hospitalized patients were included if they had symptoms, pyuria and bacteriuria with ≥10^5 CFU/ml Gram-negative uropathogens that were susceptible to the study drugs. Combined clinical and microbiological response was 73% with cefiderocol and 55% with imipenem–cilastatin, demonstrating non-inferiority of cefiderocol ($P = 0.0004$). Microbiological response was 73% with cefiderocol and 56% with imipenem–cilastatin. A post hoc statistical analysis of this end point confined to CIs was interpreted as a superior response. Observed treatment differences were rather high; therefore, a clinical benefit for cefiderocol, especially in infections with pathogens resistant to other broad-spectrum agents, might be present.

IGNITE3

The phase III IGNITE3 study compared eravacycline (1.5 mg/kg body weight 24-hourly) with ertapenem (1 g 24-hourly) in 1,205 patients with cUTI. Treatment duration was 5–10 days, and oral step-down was possible after 5 days of intravenous treatment[104]. The co-primary end points were a combination of clinical cure and microbiological success in the mMITT population at the end of intravenous treatment and at the TOC visit. Combined clinical and microbiological response rates at the TOC visit were 68.5% for eravacycline and 74.9% for ertapenem. As the 95% CI was −12.6% to −0.3%, non-inferiority was not met. Owing to this non-inferiority result, eravacycline has not been approved for cUTI treatment by the FDA.

ZEUS

The phase II/III ZEUS study compared fosfomycin (intravenous 6 g 8-hourly) with piperacillin–tazobactam (4.5 g 8-hourly) in 465 patients with cUTI or pyelonephritis[105]. Treatment duration was 7–14 days. The primary efficacy end point was the composite of clinical response and microbiological response at the TOC visit for the mMITT population. Combined clinical and microbiological response was 64.7% for fosfomycin and 54.5% for piperacillin–tazobactam, demonstrating the non-inferiority of fosfomycin. A post hoc analysis was carried out redefining microbiological eradication by molecular genotyping and resulted in a quasi-superior outcome in favour of fosfomycin. This can be explained by the fact that, traditionally, microbiological eradication is evaluated at the species level based on eradication of the bacterial species that is initially present. Applying molecular typing, eradication in this post hoc analysis was based on clonal level. If the initially present bacterial clone was eradicated, this was accepted as eradication.

RESTORE-IMI1

The phase III RESTORE-IMI1 study compared imipenem–relebactam (750 mg 6-hourly) with colistin (150 mg 12-hourly; loading dose 300 mg) plus imipenem alone (500 mg 6-hourly) in 47 patients with imipenem-non-susceptible infections, 16 of whom had cUTI or pyelonephritis[106]. Treatment duration was 5–21 days. The primary end point for patients with cUTI or pyelonephritis was a composite clinical and microbiological response at early follow-up, 5–9 days following the end of therapy in the mMITT population. Combined clinical and microbiological response in the patients with cUTI or pyelonephritis was 72.7% with imipenem–relebactam and 100% with imipenem–colistin, demonstrating the non-inferiority of imipenem–relebactam to imipenem–colistin (95% CI −52.8 to 12.8). Infections with carbapenem-resistant pathogens are challenging to treat and patients with such infections are difficult to recruit. In this study, there was no statistical difference between the two arms. Therefore, imipenem–relebactam received FDA approval for the treatment of cUTI.

EPIC

The phase III EPIC study compared plazomicin (15 mg/kg body weight 24-hourly) with meropenem (1 g 8-hourly) in 609 patients with cUTI or pyelonephritis[107]. Treatment duration was 7–10 days, with an optional oral step-down possible after 4 days of intravenous therapy. The primary end point was the composite of clinical response and microbiological response at day 5 and the TOC visit for the mMITT population (at least one qualifying baseline pathogen that was susceptible to both meropenem and plazomicin). At day 5, composite cure was 88.0% for plazomicin and 91.4% for meropenem, confirming the non-inferiority of plazomicin (95% CI −10.0 to 3.1). At the TOC visit, composite cure was 81.7% for plazomicin and 70.1% for meropenem, demonstrating the superiority of plazomicin (95% CI 2.7–20.3). According to the prespecified primary end point, plazomicin was non-inferior to meropenem. This study especially excluded patients from the mMITT population who had pathogens that were resistant to the comparator; thus, results were not biased towards plazomicin. This study also showed that monotherapy with an aminoglycoside plazomicin is effective in the treatment of cUTI.

In summary, these studies showed non-inferiority of novel drugs compared with current standard-of-care agents, suggesting that these tested drugs can be used for treatment of cUTI and pyelonephritis, including in the context of increasing antimicrobial resistance. However, these novel substances should be used cautiously as antibiotics of last resort, in order to avoid the development of resistance for as long as possible.

Issues with patient populations

The populations selected for the evaluation of the primary outcome criteria varied in these studies. For example, in some studies, only patients with infections caused by Gram-negative organisms were included, whereas in other studies, only those patients with causative uropathogens susceptible to the study drugs were included. However, most patients were enrolled on an empirical basis, as treatment of cUTI and pyelonephritis needs to be started immediately and empirically in most cases. Non-evaluable patients are therefore excluded post hoc. Consequently, the primary evaluable population is often substantially smaller than the ITT population (BOX 1). In addition, the patient study visits also differed, as they were designed according to

the primary outcome criterium, for example, if oral step-down antibiotic treatment was allowed or not. Most recent interventional studies include a co-primary end point consisting of improvement of symptoms and eradication of bacteria in the urine, which is in line with FDA and the revised EMA guidance[32,33]. However, in contrast to uncomplicated cystitis, for which validated questionnaires exist to objectively evaluate symptoms and symptomatic response[108,109], these are not available for cUTI and pyelonephritis and should be developed to enable objective assessment of clinical symptoms in patients.

Future directions

An important question is how clinical trial designs can be developed further to provide data that allow better comparison of trial populations and improve translation of results to the clinically heterogenous population of patients with cUTI or pyelonephritis.

Clinical trials of novel treatments

Despite disparities in the patient cohorts in these clinical studies of novel agents, most novel antibiotics with activity against Gram-negative bacteria that have been studied in patients with cUTI or pyelonephritis provide highly interesting data, showing the efficacy of various antibiotic substances with or without combination with beta-lactamase inhibitors in a time of increasing antibiotic resistance, whereas eravacycline has failed to show non-inferiority to the comparator. It is certainly understandable that early phase II or even phase III studies are performed in a homogeneous patient population, mainly excluding patients with chronic indwelling urinary catheters, for example. However, future phase II and phase III studies should be conducted in extended patient populations that better reflect everyday clinical situations and include more severe infections, such as urosepsis. At a minimum, stratifying patients using the ORENUC classification system might clarify which disease entities have been included in a study and which have been excluded (TABLE 1; FIG. 2).

The classification of UTIs into uncomplicated and complicated is still useful and valid, although the boundary between the two entities is flexible[27,28,34,35]. The design of studies to test treatments for cUTI and pyelonephritis is gradually changing, to more frequently include symptomatic response instead of solely a microbiological outcome. As symptoms are part of the primary outcome criteria in the FDA and draft revised EMA guidance[32,33], a concerted effort should be made to objectively assess symptoms, as for the validated symptom questionnaires that have been developed for uncomplicated UTI[108,109]. This would help to obtain standardized results. Previously reported studies are almost exclusively non-inferiority analyses. Attempts should be evaluated to target superiority analyses, at least in certain patient groups. Currently, stratification is usually based only on anatomical location of the infections (lower versus upper UTIs) but not on risk factors[21] such as upper urinary tract obstruction versus no obstruction, urological risk factors versus nephrological risk factors, or modifiable versus permanent risk factors. In addition, emergence of antibiotic resistance in specific microbiological compartments (for example, the gut microbiota), should at the very least be included as a secondary outcome criterium. In cases in which only infections with specific bacterial species or antibiotic resistance features are included in the evaluable population, point-of-care testing for bacterial species and point-of-care susceptibility testing should be included in the study design[110].

Treatment of other infections

The trials of new antibiotics with potential activity against resistant and multidrug-resistant pathogens are mainly designed to demonstrate the non-inferiority of these agents versus standard of care in various indications. The pathogens in the majority of included patients will not be multidrug-resistant organisms and patients who are likely to be treated with these antibiotics are frequently excluded. Most antibiotics that are active against Gram-negative bacteria are tested in cUTI and pyelonephritis and usually include large patient populations. The data obtained in these trials comprise microbiological data on various bacterial species with different levels and mechanisms of resistance and on how the antibiotic substance acts clinically. The ensuing pharmacokinetic and pharmacodynamic data comprise valuable information not only about dosage, bacterial spectrum and clinical spectrum but also about adverse effects, which can be exploited for treatment of infections in other locations and those in special patient groups, such as patients with impaired renal function.

Conclusions

Current UTI classification systems are heterogeneous and do not enable detailed evaluation of patients who are at risk of recurrence or treatment failure. Thus, novel classification systems, such as the ESIU ORENUC risk classification system, should be further evaluated and adopted. UTIs are a very important model system for studying various aspects of infections. In the past decade, almost all novel antibiotics that are active against Gram-negative bacteria have been tested in UTIs or pyelonephritis. The advantages that are offered by UTI as a model system, such as easy access to urine as the primary diagnostic source or the high frequency of infections, are not yet fully exploited. The heterogeneous bacterial composition in patients with cUTI or pyelonephritis who are evaluated in clinical studies produces abundant information on clinically important bacteria, such as *E. coli* (and other Enterobacteriaceae), *P. aeruginosa* and enterococci (if not excluded from the study population), in terms of resistance data and treatment responses. The different study designs should be adapted to modern requirements, such as treating antibiotic-resistant and multidrug-resistant pathogens, involving superiority designs, including difficult-to-treat patient cohorts with severe infections and evaluating the emergence of antibiotic resistance in compartments such as faeces.

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This paper provides a review of emerging point-of-care test systems in UTI.

Author contributions

All authors researched data for the manuscript, made substantial contributions to discussions of content, wrote the manuscript, and reviewed and edited the manuscript before submission.

Competing interests

F.M.E.W. declares personal fees from Achaogen, AstraZeneca, Bionorica, Janssen, Leo Pharma, MerLion, MSD, OM Pharma/Vifor Pharma, Pfizer, RosenPharma, Shionogi, VenatoRx and GSK. F.M.E.W declares research grants from Bionorica, Enteris BioPharma, Helperby Therapeutics, OM Pharma/Vifor Pharma, Shionogi and Deutsches Zentrum für Infektionsforschung (DZIF) (Giessen-Marburg-Langen site). The other authors declare no competing interests.

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