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Urinary Tract Infection

The Result of the Strength of the Pathogen, or the Weakness of the Host

Edited by Tomas Jarzembowski, Agnieszka Daca and Maria Alicja Dębska-Ślizień

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Notice

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Meet the editors

Tomasz Jarzembowski was born in 1968 in Gdansk, Poland. He obtained his PhD degree in 2000 from the Medical University of Gdańsk (UG). After specialization in clinical microbiology in 2003, he started studying biofilm formation and antibiotic resistance at the single-cell level. In 2015, he obtained his DSc degree. His later study in cooperation with experts in nephrology and immunology results in the designation of the new diagnostic method of UTI, patented in 2017. He is currently working at the Department of Microbiology, Medical University of Gdańsk (GUMed), Poland. Since many years, he is a member of steering committee of Gdańsk branch of Polish Society of Microbiologists, a member of ESCMID, a member of editorial board of international journals, and a reviewer.

Agnieszka Daca was born in 1982 in Świecie, Poland. She prepared and defended her PhD degree thesis in 2011 from the Medical University of Gdańsk and discussed the immunological changes observed in the blood of patients with SLE. After her PhD degree defense, the cooperation of Tomasz Jarzembowski and the experiments characterizing bacteria virulence traits and their interaction with immune system cells have started, resulting in the designation of diagnostic method assessing virulence potential of bacteria isolated from the urine of immunocompromised patients. These experiments have also turned her attention to innate immune system changes in patients with lupus nephritis. Currently, she is working as an assistant professor at the Department of Pathology and Experimental Rheumatology, Medical University of Gdańsk. She is also a member of ESCMID.

Professor Maria Alicja Dębska-Ślizień works in the field of nephrology and transplantology since 1985. She is the head and the chair of the Department of Nephrology, Transplantology, and Internal Medicine, GUMed, since 2015. She is a specialist in the field of internal diseases, nephrology, and clinical transplantation. Her fundamental topics of clinical and scientific interest are optimization of the treatment of patients with renal failure by means of kidney transplantation (preemptive transplantation, transplantation from living donors). She has an active participation in the European Rare Kidney Disease Reference Network (i.e., congenital glomerulopathy, TSC, ADPKD). Her other activities include optimization of hemodialysis treatment, nephro-oncology, and coordination with the Polish Renal Replacement Therapy Registry. She is a member of the Polish Society of Nephrology,

the Polish Transplantation Society (secretary-general), and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). Currently, she is also a member of the main board of the Polish Society of Nephrology and the Polish Transplantation Society. She is an author and coauthor of about 500 publications in domestic and foreign magazines. She is an editor and coeditor of the monograph and several guides for the sick and dozens of chapters in textbooks. She is a lecturer in Polish and international congresses. She has been awarded numerous prizes for both her native university and the Polish Transplantation Society for her scientific activity. Her closest family is her husband and two children (daughter and son). Her nonprofessional interests are mountain climbing, skiing, and reading books.

Contents

Foreword

Urinary tract infections (UTIs) belong to high frequently occurring diseases causing big discomfort for patients and often disabling their daily job duties. UTIs are one of the most frequent reasons for medical interventions, they generate 40% of all hospital infections, and additionally, they induce 10% to 20% of posthospital infections. The disease occurs 50 times more frequently in females than in males. UTI appears in various manifestations; there is a need to define uniform terminology connected with this disease for easier recognition of the disease and to undertake proper decision to choose a suitable course of the therapy process.

UTIs are caused by various infectious agents in terms of etiological factors, such as bacteria and fungi, such that *Candida albicans* responsible for candidiasis, *Schistosoma* spp. responsible for schistosomiasis (bilharziasis), *Actinomyces israelii* (*A. bovis*) responsible for actinomycosis, nematodes from genera *Wuchereria bancrofti* and *Brugia malayi* responsible for filariasis, or *Echinococcus granulosus* responsible for echinococcosis. Gram-negative rods from family *Enterobacteriaceae* with dominated uropathogenic strains of *Escherichia coli* (UPEC) are the most frequently reported etiological factors of UTI. These strains are responsible for 85% cases of uncomplicated infections and 45% cases of complicated infections. There are also the other Gram-negative bacteria responsible for UTI such as *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Providencia* spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp., and from the Gram-positive group, they are *Staphylococcus aureus*, *S. saprophyticus*, *Streptococcus agalactiae*, *Enterococcus* spp., and *Corynebacterium urealyticum*. The dominating bacteria causing in-hospital infections are *E. coli* (50%) and then in order *Enterobacter* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Serratia marcescens*, *Providencia* spp., *Staphylococcus* spp., *Enterococcus* spp., and fungi. Interestingly, most of these bacteria are constituents of the physiological biocenosis in the intestinal tract or urinary-sexual systems in human; therefore, UTIs are mostly endogenous infections. What is interesting too is that although the etiology of UTI did not change in the last decade, the recent bacterial pathogens acquired a set of new characters, which implicate difficulties in effective therapy. The most important new property of the strains is acquisition of antibiotic resistance mechanisms and of new virulence genes through horizontal gene transfer (HGT). The emergency of new bacteria phenotypes is reported too. The other properties such as biofilm formation and mobile genetic elements (MGEs) additionally obstruct both diagnosis and therapy.

Furthermore, an increased risk of UTI is caused by physiological factors like advanced age of patients or pregnancy and also by pathological factors such as systemic diseases, interference with instrumentation of urinary tracts, immunosuppressive agents, or diabetes.

UTIs are complex and dynamic pathologic phenomena, and the number of UTI patients remains high. A group of UTI is involved into two big global phenomena, namely, a quick increase of antibiotic resistance of pathogens and the emerging of new biochemical phenotypes of bacteria that enhance virulence and cause diagnostic problems.

New diagnostic methods are introduced particularly to recognize microbiological etiological factors, but both diagnosis and therapy require strict cooperation among leading doctor, microbiologist diagnostician, and clinical pharmacologist.

UTIs are still a big challenge for medicine demanding systematic epidemiologic reports and research study to improve their diagnostics and therapy process. That is the reason why various forms of studies published as original papers, monographs, and recommendations are needed and expected by practitioners. The presented book is an attempt to answer these demands.

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Preface

Urinary tract infection (UTI) is a problem so common and so significant in routine clinical practice that accurate diagnostics are especially important. The first milestone in the diagnostics of UTI was set almost 60 years ago, when the definition of significant bacteriuria was intended by Kass to provide a means of differentiation between contamination of urine and true urinary infection. Until now, the gold standard for the diagnosis of UTI is the estimation of inoculum of bacteria in the urine sample. According to this assumption, the number of bacteria (cfu/mL) smaller than 10^5 cfu/ml is likely to result from contamination from the urethral meatus. However, this threshold may miss many relevant infections. Nowadays, therefore, there are other recommendations for the diagnosis of UTI from a count of 10^3 cfu/mL, depending on the types of bacteria detected and clinical conditions. Additionally, the quantitative character of the diagnostic procedure requires proper conditions, sampling, and transport, which may be difficult to complete in routine practice. As a result, diagnostics may suffer from prelaboratory errors. Furthermore, apart from detection of the pathogen in urine, the presence of clinical symptoms is also essential.

UTI incidence depends on many factors, e.g., age, gender, and accompanying diseases. From a clinical point of view, the most demanding groups of UTI patients are the people with compromised immune systems. The incidence of UTI is high in this group, both due to the impaired functioning of the immune system and the frequent presence of additional medical devices, such as catheters. The presence of catheters in itself increases in turn the risk of the development of a complicated UTI. Complicated UTI is associated with an increased rate of therapy failures, as a result of possible biofilm formation on foreign elements and antibiotic resistance, as well as the increased possibility of an infection recurrence. The higher risk of complicated UTI calls for unequivocal diagnostic test results to start efficient therapy as quickly as possible, preferably at the bedside. These are the arguments for the constant search for novel diagnostic tools and techniques, which will be quicker to perform, easier to interpret, and less susceptible to preanalytical errors.

What makes UTI so inspiring, and engages so many outstanding scientific teams in relentless work on the topic, is the development of new techniques, which allow us to explore ever newer aspects of bacterial and human life mechanisms. It allows us to discover much more bacterial survival strategies dictated by the evolution-driven will of survival on the one hand and the human body's ways to defend itself against these novel invasions on the other hand. The balance between these two elements—bacterial desire to colonize the human's body and man's wish to survive—seems to be what allows us to exist in continuous cohabitation, but it can also lead to the failure of even the best-planned treatment.

These as well as many other vital topics regarding UTI complications, management, and treatment, in addition to antibiotic resistance and bacterial virulence traits allowing us to mitigate or avoid antibiotic action, are presented in this book.

Each and every one of the authors contributing in this publication performed an excellent work for which we are grateful and hope that every reader of this book will find something inspiring in it.

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Chapter 1

Management of Complicated Urinary Tract Infection

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Abstract

The management of complicated urinary tract infection (UTI) remains a challenge since the coexisted conditions may significantly decrease the successful rate of treatment. In this chapter, the specific conditions including indwelling catheter, urolithiasis, neurogenic bladder, vesicoureteral reflux and pregnancy are listed. In terms of each condition, the potential influence on UTI and management strategy is discussed. Not only is the current evidence reviewed but also we present our experience on management of complicated UTI.

Keywords: urinary tract infection, catheter, urolithiasis, neurogenic bladder, vesicoureteral reflux, pregnancy

1. Introduction

Urinary tract infection (UTI), defined as an inflammatory response of the urothelium induced by a pathogenic organism, is one of the most common infectious diseases. It is estimated that one-third of the women may experience UTI by the age of 24, and half of the women suffer from at least one symptomatic UTI during their lifetime [1]. Basically, UTI can be classified as uncomplicated and complicated infection. The former is normally confined to bladder, which can be treated by short-course antibiotics. The latter refers to an infection associated with a condition which can increase the rate of therapy failures significantly. It is reported that 25–30% of adult women with UTI have at least one risk factor causing complicated UTI [2]. The common conditions which may result in complicated UTI are presented in **Table 1**. Not only do these factors decrease treatments' successful rate but also increase the recurrence risk of UTI. Therefore, when a complicated UTI is treated, management of the conditions needs to be taken into consideration.

Category	Specific conditions
Foreign bodies	Indwelling catheter
	Urolithiasis
Structural or functional abnormality of urinary tract	Neurogenic bladder
	Vesicoureteral reflux
	Obstructive uropathy
Others	Pregnancy
	Diabetes mellitus
	Renal failure
	Immunosuppression after kidney transplantation

Table 1. Specific conditions causing complicated UTI.

2. Catheter-associated UTI

Catheter-associated UTI is one of the most common complicated UTIs. It has been reported that catheter-associated UTI may lengthen the patients' hospital stay and increase the mortality and the direct medical cost [3, 4]. Typically, the microorganisms can enter urinary tract through the extraluminal or intraluminal route. The former means microbial pathogens can invade the bladder through the gap between the catheter and urethra, whereas the latter indicates that causative agents migrate to bladder along the internal lumen of the catheter. According to the data from National Healthcare Safety Network (NHSN), the top three pathogens causing catheter-associated UTI are *Escherichia coli* (21.4%), *Candida spp.* (21.0%) and *Enterococcus spp.* (14.9%), followed by *Pseudomonas aeruginosa* (10.0%), *Klebsiella pneumoniae* (7.7%) and *Enterobacter spp.* (4.1%) [5]. With the duration of catheterization prolonging, the pathogens may induce the formation of biofilm on the surface of the catheter, which causes the occurrence of antibiotic resistance [6]. Traditionally, antimicrobial therapy was considered as a prevention strategy for catheter-associated UTI. However, a survey in two Dutch district hospitals showed that the use of antibiotics was associated with the development of bacteriuria in patients catheterized for 3–14 days [7]. A recent cohort study further revealed that empirical antibiotic treatment had no effect on patients' prognosis [8]. Both European Association of Urology (EAU) and Infectious Diseases Society of America (IDSA) guidelines recommend against the use of systemic antimicrobial prophylaxis for catheter-associated UTI [9, 10]. By contrast, the consistent recommendation identified across guidelines is removal of the catheter as soon as possible. However, some patients have to be catheterized for a long time due to various disorders. For those patients, some practical strategies are developed to prevent and manage the catheter-associated UTI.

2.1. Alternatives to indwelling urethral catheter

Instead of indwelling urethral catheterization, some alternative approaches have been developed to minimize the catheter-associated UTI. Those approaches include use of external

catheter, intermittent catheterization and suprapubic catheterization. Condom catheter is the most common external equipment, which is suitable for patients with severe storage lower urinary tract dysfunction such as urinary incontinence. It has been reported that condom catheter has a significant advantage in comparison with indwelling catheter. A randomized controlled trail (RCT) demonstrated that condom catheter might reduce 80% risks of catheter-associated UTI or death compared to indwelling catheter. Additionally, patients with condom catheter presented a significant higher satisfaction rate than ones with the indwelling catheter [11].

For patients with severe voiding lower urinary tract dysfunction, intermittent or suprapubic catheterization is an option to replace indwelling catheter. An early study investigated the incidence of bacteriuria in patients with intermittent or indwelling catheterization. Based on the results of urine culture, 32% of patients treated with intermittent catheterization had bacteriuria, which is significantly lower than 61% in ones with an indwelling catheter [12]. Another study revealed that patients with intermittent catheterization had less chance to suffer from pyelonephritis than the counterparts with indwelling catheterization (5 vs. 25%, $P < 0.01$) [13]. In a multicentered RCT, 87 patients with a postvoid residual (PVR) bladder volume of more than 150 ml were allocated to receive intermittent or indwelling catheterization. After 3 days, a significant lower risk of developing bacteriuria was found in the intermittent catheterization group compared with the indwelling catheterization group (14 vs. 38%, $P = 0.02$), so was the risk of UTI (12 vs. 33%, $P = 0.03$). In terms of patients' satisfaction, no marked difference was found between these two groups [14].

In general, intermittent catheterization can be practiced by a clean or sterile technique. Originally, sterile intermittent catheterization was applied as a standard method. In 1947, Guttman published the first report about sterile intermittent catheterization. In the report, he showed that this technique could decrease the risk of UTI and might be helpful for patients' recovery of micturition. About 19 years later, Guttman further reported his experience in the use of sterile intermittent catheterization. During 11 years, he applied this technique to manage a total of 476 patients. Based on the data from 409 males, the technique was related to an extremely low incidence in UTI, vesicoureteral reflux, hydronephrosis and urolithiasis. Although sterile intermittent catheterization has some advantages, it is costly and time-consuming. In 1970, Hence Lapides and Betty S. Lowe introduced another technique, that is, clean and intermittent self-catheterization. Subsequently, they published a series of articles in which they showed that this technique could not increase the incidence of UTI. Later, a number of emerged evidence suggested that sterile intermittent catheterization could not provide an extra benefit compared to clean techniques. Two RCTs demonstrated that different technique was associated neither with overgrowth of microorganisms in urinary tract nor with the symptomatic UTI [15, 16].

Suprapubic catheterization provides a treatment option for patients who are not suitable for intermittent catheterization such as those with low compliance bladder. Evidence has illustrated that suprapubic catheter may bring more benefits for patients compared to transurethral catheter. A retrospective cohort study showed that patients with suprapubic catheter had less clinical visits due to pain than ones with indwelling urethral catheter [17]. The result from a meta-analysis revealed that suprapubic catheterization was associated with a significant lower risk of

bacteriuria and less discomfort compared with transurethral catheter [18]. A prospective open-labeled study presented that women with postoperative urinary retention favored suprapubic catheter due to a better catheter-specific quality of life [19]. According to the result from a network meta-analysis, indwelling urethral catheter did not increase the risk of UTI compared with either suprapubic tube or intermittent catheterization when duration of catheter was less than 5 days. In contrast, suprapubic tube or intermittent catheterization was associated with a lower rate of UTI when long-term catheterization is needed [20]. Based on our experience, suprapubic catheter has a significant advantage for male patients. We used suprapubic catheter to manage more than 20 male patients who suffered from recurrent acute bacterial prostatitis or epididymitis secondary to indwelling urethral catheter. We found that no one experienced these genitourinary infections again after the technique of catheterization was changed. Additionally, suprapubic catheter allows patients to observe their recovery of voiding function. We encourage patients to try to urinate with a closed suprapubic catheter if they have a low detrusor leak-point pressure (<40 cmH_20) assessed by urodynamics, which means patients' attempt of voiding cannot bring about upper urinary tract deterioration. After spontaneous voiding, patients need to open the suprapubic catheter and measure the PVR. Once the PVR is low enough, the removal of suprapubic catheter can be taken into consideration.

2.2. Catheter selection

To prevent the catheter-associated UTI, some special catheters have been designed and developed. They mainly include silver-coated, antibiotic-coated, hydrophilic and novel trefoil catheters.

As is known, silver is a kind of antiseptic. So it was hypothesized that catheter coated with silver could reduce the risk of UTI in patients treated by the indwelling catheter. Based on this hypothesis, a variety of silver-coated catheters have been developed. However, the efficacy of these catheters on UTI prevention varies from one to another. Evidence showed that silver alloy-coated catheter might reduce the incidence of UTI, but the silver oxide-coated one would not. A prospective single-center study conducted in Hong Kong investigated the incidence of UTI in patients with a silver alloy and hydrogel-coated catheter, which was compared with the counterparts with a standard catheter. The results showed that the incidence of UTI per 1000 catheter days was 6.4 and 9.4 in the silver-coated catheter group and standard catheter group, respectively. The silver-coated catheter group presented a 31% reduction in risk of UTI [21]. Lederer et al. reported the similar results in a retrospective cohort study in which 7 medical centers with 2778 active acute care beds in the United States were involved. They found that the silver alloy and hydrogel-coated catheter could cause a 47 and 58% relative reduction in UTI rate, respectively, compared to the conventional catheter when a different definition was applied [22]. In contrast, two clinical trials revealed that the use of silver oxide-coated catheter could not reduce the incidence of UTI and bacteriuria in comparison with standard catheter [23, 24]. Besides the two silver-coated catheters mentioned earlier, another silver nanoparticle-fabricated catheter has been developed. According to an experimental study, this silver nanoparticle catheter had significant antimicrobial and antibiofilm properties, as well as a remarkable ability to cause disorganization of bacterial cell membrane, which may prevent UTI effectively [25].

It has been shown that antibiotic-coated catheter has a significant antimicrobial activity. Desai et al. found that nitrofurazone-impregnated catheter could decrease the adherence of pathogenic microorganisms to catheter markedly, but the effect could only persist for 5 days after the catheterization [26]. Regev-Shoshani et al. further reported that both nitrofurazone- and nitric oxide-coated catheters had a great effect on the prevention of microbial growth and biofilm formation, which was more effective than silver-coated catheter [27]. Despite lack of available clinical data so far, the antibiotic-coated catheter may bring potential benefits for patients with indwelling catheter.

Hydrophilic catheter may decrease the friction between catheter and urethra during catheterization. Consequently, it reduces the potential mucosal trauma which can result in the bacterial colonization. A multicentered RCT showed that the use of hydrophilic catheter might decrease approximately one-third the risk of developing symptomatic UTI compared with standard catheter [28]. Similarly, the evidence from a meta-analysis supported marked benefits of hydrophilic catheter in terms of the incidence of UTI [29].

A novel trefoil catheter has been developed. Although it has not been reported for use in clinical practice, the preclinical study has shown its advantages. Sun et al. performed an experiment in which 66 rabbits were catheterized using either conventional or novel trefoil catheter randomly and reported that the novel catheter could decrease the incidence of bacteriuria. In addition, it was also found that the trefoil catheter caused a significant slighter mucosal inflammation than conventional catheter based on endoscopic assessment [30].

2.3. Catheter care

Catheter care is important for patients with an indwelling catheter since appropriate care can decrease the incidence of UTI. Both EAU and IDSA guidelines recommend maintaining a closed drainage system all the time [9, 10]. Once any breaks are detected, both the catheter and collecting system must be replaced as soon as possible. Besides, it is crucial to keep the drainage tubing being below the level of the patient's bladder and above the level of the collection bag, which can avoid the reflux of urine in drainage system. To minimize the risk of UTI, different types of collecting systems were developed. However, current evidence fails to show their different effects on prevention of UTI. Sullivan et al. conducted a RCT, in which 51 hospitalized dogs were catheterized with either an open or closed urine collection system. After analyzing the incidence of bacteriuria, they concluded that the type of urine collection system (open vs. closed) was not associated with the risk of developing bacteriuria [31].

In terms of the time point to change catheter, most guidelines recommend against changing catheter routinely. Instead, it is recommended to change the catheter before blockage occurs. Furthermore, some strategies including bladder irrigation with citric acid solution and oral acetohydroxamic acid have been proven to be effective for prevention of catheter blockage [32, 33]. By contrast, bladder washing with saline is not recommended due to lack of effectiveness [34].

3. Urolithiasis

Urolithiasis is one of the most common urological diseases with a rising incidence around the world. In general, UTI is usually considered as a complication of urolithiasis. Actually, it is also a potential pathogenic factor for a special urinary stone, struvite. Basically, the formation of struvite originates with the bacterial decomposition for urea. Some bacteria, including Proteus and Klebsiella, can decompose urea into ammonia and carbon dioxide, which can be further converted into ammonium and bicarbonate, respectively, and consequently, elevate the pH value of urine. With an alkaline urinary environment, the ammonium has a strong ability to combine with magnesium and phosphate. Once these chemical substances become supersaturated in urine, they will crystallize and deposit the struvite. The existence of urinary stone, especially struvite, may cause UTI difficult to treat because the stone may act as a nidus for microorganisms and result in obstruction in urinary tract.

According to our experience, when UTI and urolithiasis coexist, the individualized management strategy should be taken into consideration. If the stone causes a urinary tract obstruction, the initial treatment should focus on the decompression of the collecting system, which can avoid the infection being exacerbated. Normally, the best way of decompression is to remove the stone as soon as possible, which can be achieved either by ureteroscopic lithotripsy or by percutaneous nephrolithotripsy. However, if the patient cannot tolerate these minimally invasive surgeries, indwelling ureteral stent and percutaneous nephrostomy tube could be the optional treatment. Only with an unobstructed collecting system can the subsequent antibiotic therapy for UTI be efficient. For patients with coexistence of UTI and nonobstructive stone, empiric antibiotic therapy can be the initial treatment. Only when the UTI fails to manage, the invasive intervention is considered to remove the stone.

4. Neurogenic bladder

Neurogenic bladder refers to the bladder dysfunction secondary to a certain disease of the central nervous system or peripheral nerves. The specific conditions causing neurogenic bladder are various and the most common one is spinal cord injury, followed by multiple sclerosis, cerebral vascular events and Parkinson's disease [35]. Moreover, long-standing diabetes plays an important role in the development of neurogenic bladder. It is reported that patients with neurogenic bladder have a significant increased incidence of UTI. An observational study in which 46,000 patients with neurogenic bladder were investigated and followed up showed that 29.2–36.4% of patients were diagnosed with lower UTI annually [35]. Another study revealed that 81% of patients with spinal cord injury experienced at least one UTI during a period of 5 years [36]. The etiology of UTI caused by neurogenic bladder is diverse. It is reported that the bladder ischemia and defect of glycosaminoglycan layer induced by bladder overdistension reduce the barrier function of urothelium [37, 38]. Moreover, immunological impairment of bladder mucosa involving NK cell, B and T cell further decreases the bladder's ability to defend the pathogens [39, 40].

For patients with neurogenic bladder, the clean intermittent self-catheterization is the most common technique to avoid bladder overdistension. It remains a big issue whether prophylactic

antibiotics can prevent bacteriuria and UTI in patients performing clean intermittent self-catheterization due to neurogenic bladder. Two double-blind, placebo-controlled, crossover trials showed that nitrofurantoin prophylaxis could reduce the risk of bacteriuria and UTI significantly [41, 42]. On the contrary, a Cochrane systematic review demonstrated that the evidence failed to prove the certain benefits of antibiotic prophylaxis in patients with clean intermittent self-catheterization [43]. In a recently published case series study, Cox L et al. described a successful treatment in reduction of UTI in patients with clean intermittent self-catheterization using intravesical instillations of gentamicin [44]. However, the treatment strategy needs to be further verified by well-designed RCTs.

5. Vesicoureteral reflux

Vesicoureteral reflux is the most common risk factor for UTI in children. It is reported that 30–40% of children with their first UTI episode are affected by this disorder [45, 46]. In general, vesicoureteral reflux is graded from I to V (mild to severe) according to the height of reflux up the ureter and degree of dilatation of the ureter. A high grade of vesicoureteral reflux, defined as grade IV and V, may lead to the renal scars due to UTI, which may further cause renal failure. Conventionally, antibiotic prophylaxis has been considered as the standard management for patients with vesicoureteral reflux. However, a large cohort study revealed that continuous antibiotic prophylaxis could not decrease the risk of recurrent UTI but might increase the risk of bacteria resistant to the antibiotic in children with vesicoureteral reflux [47]. As an approach to eliminate reflux, some invasive interventions including anti-reflux surgery and injection of bulking agent are used to reduce the breakthrough UTI. Basically, the surgical options include open or laparoscopic ureteral reimplantation. Based on clinical assessment, the reported successful rate for open and laparoscopic approach is 80–95% and 90–93%, respectively [48–50]. In contrast, the endoscopic injection presents a lower treatment successful rate in the range of 50–93% [48]. From our experience, surgical intervention may be an effective therapy for the patients who still suffer from UTI even on continuous antibiotic prophylaxis.

6. Pregnancy

It is reported that pregnant women have an increasing risk of UTI, especially upper UTI, because the physiological changes induced by pregnancy make them more likely to suffer from pyelonephritis. On the one hand, elevated level of progesterone during pregnancy can induce the relaxation of ureteric smooth muscles, which may lead to the urine retention in the renal collecting system and ureter. On the other hand, the noticeable increase in renal blood volume and glomerular filtration rate may contribute to the renal pelvic and ureteral dilation. The dilated upper urinary tract provides pathogens with a permissive environment to grow and reproduce. As a result, bacteriuria will develop pyelonephritis in 25–40% of pregnant women. The independent risk factors include history of UTI, low socioeconomic status, indigence, intercurrent diabetes and sickle cell trait. Therefore, short-course antibiotic therapy should be applied to prevent developing ascending UTI, once the bacteriuria is identified in pregnant

women. It is investigated that the antibiotic therapy can reduce the incidence of pyelonephritis by 75% [51]. Generally, a three-day course of antibiotic therapy directed by urine culture is recommended for both symptomatic lower UTI and asymptomatic bacteriuria. When the result of culture is not available, an empiric therapy with a ß-lactam or nitrofurantoin can be used as the initial treatment. For patients with upper UTI, a 14- to 21-day course of intravenous antibiotic therapy should be adopted. The reported effective antibiotic includes a third-generation cephalosporin, gentamicin or aztreonam, which can be used as the initial treatment before the result of culture is available. In addition, it is crucial to identify whether an obstruction exists in every pregnant woman. Once the obstruction is diagnosed, it can be relieved by ureteral stent or percutaneous nephrostomy tube. For patients with ureteral stent or percutaneous nephrostomy tube, it is necessary to use the antibiotic continuously until after delivery.

7. Conclusion

The treatment of complicated UTI remains a challenge because the coexisted conditions are diverse. Appropriate management for these conditions is the prerequisite achieving a successful treatment for complicated UTI.

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Conflict of interest

None.

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Chapter 2

Management of Urinary Tract Infections: Problems and Possible Solutions

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Abstract

In clinically suspected urinary tract infections (UTIs), empirical antibiotic treatment is usually started long before the laboratory results of urine culture and antibiogram are available. Although molecular diagnostic approaches are being applied to the diagnosis of many infections, UTIs are generally diagnosed by traditional culture methods. Patient care could greatly benefit from the development of a rapid, accurate, inexpensive test that could be done at patient's bedside, allowing the practitioner to plan targeted, more effective therapy. Such a test would potentially reduce incorrect or unnecessary use of antibacterial drugs and reduce the emergence of bacterial resistance. In response to this pressing and unmet clinical need, several methods have been developed in the last few years. Among these, the new point-of-care test (POCT) for detecting UTIs named Micro Biological Survey (MBS) UTI CHECK holds promise, as it allows semi-quantitative determination of bacterial load in urine leading to a fast detection of UTIs and to evaluation of bacterial antibiotic susceptibility. This new technology operates through a colorimetric survey performed in low-cost, ready-to-use, disposable vials, in which 1 ml of urine is inoculated without any preliminary treatment and requiring neither specialized personnel nor a specialized equipment.

Keywords: urinary tract infections, point-of-care test, clinical microbiology analysis, UTIs diagnosis, antimicrobial resistance

1. Introduction: definition and background over urinary tract infections (UTIs)

Urinary tract infections (UTIs) are caused by the presence and multiplication of microorganisms in the urinary tract, sometimes spreading to the bloodstream and possibly resulting in several clinical syndromes (e.g., pyelonephritis, cystitis, urethritis, epididymitis and prostatitis) [1].

Most UTIs are caused by bacteria, and when they occur in the urine without causing symptoms, this condition is called asymptomatic bacteriuria; when growth of bacteria leads to a panel of symptoms, this condition is referred to as symptomatic bacteriuria [1]. Urinary tract infections can manifest as bacteriuria with limited clinical symptoms and sepsis, depending on localized or systemic extension [2].

The onset of UTIs is mostly due to the ascent of microorganisms from the urethra, especially organisms of enteric origin, e.g., *Escherichia coli*, which is the causative pathogen in 70–95% of acute, uncomplicated UTIs in adults, followed by other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* spp., and by *Staphylococcus saprophyticus* in 5–10% of cases [2]; hence, the higher frequency of UTIs in women than men, depending on anatomic structure, and the increased risk of infection following bladder catheterization, which compromises natural defense mechanisms. A small fraction of UTIs can have hematogenous origin, and usually involve a few relatively uncommon microorganisms (e.g., *Staphylococcus aureus*, *Candida* spp., *Salmonella* spp. and *Mycobacterium tuberculosis*), which cause primary infections elsewhere in the body and thus reach the urinary tract [2].

UTIs are among the most prevailing infectious diseases with a substantial financial burden on society [3]. The incidence of community-acquired UTIs is highest in young women [1]: almost half of all women will experience at least one episode of UTI during their lifetime, and nearly 1 in 3 women will have had at least one episode of UTI by the age of 24 years [2]. Urinary tract infection incidence increases with age for both sexes. It is estimated that 10% of men and 20% of women over the age of 65 years have asymptomatic bacteriuria [1].

Reports from European countries and the USA show that ca. 15% of all community-prescribed antibiotics are dispensed for UTIs [3]. UTIs account for many annual hospital admissions, especially among the elderly: in the UK, the number of emergency admissions of older people with a primary diagnosis of UTI showed a 200% increase from 2001/2002 to 2012/2013, parallel to a related increase in bed days, which both are the second highest increase (in absolute terms) among groups of conditions [4]. Nevertheless, UTIs are believed to have been greatly overcoded in recent years: part of the increase may be due to changes in coding practice, part to increased emergence of antibiotic resistance [4]. Moreover, UTIs represent at least 40% of all hospital acquired infections and most of them occur following catheterization, which is considered one of the main risk factors associated to onset of UTIs [3].

2. Current laboratory standards in UTI diagnosis

The clinical evidence of UTI is based on a number of basic criteria, including clinical symptoms, and laboratory data which should provide evidence of the presence of microorganisms by culturing of urine samples, or other specific tests [2]. However, the diagnosis of UTIs is primarily based on symptoms and signs. Tests that suggest or prove the presence of bacteria or white cells in the urine may contribute additional information to inform management

but rarely have important implications for diagnosis, also considering the long time often required for obtaining results with traditional methods [5].

The gold standard for diagnosis of bacteriuria is culture of appropriate urine sample [6, 7]. Sampling by needle aspiration minimizes the risk of contamination, while catheter and midstream sampling show a higher risk of contamination and therefore yield more false positive results [5]. However, needle aspiration is invasive and midstream sampling is preferred in clinical practice [8]. Routine culture is generally carried out streaking 10 μl of urine sample on agar plates containing selective or differential media and reading results after at least 24–48hours of incubation, considering characteristic colony morphologies and average quantitation. If there is the need for more accurate quantitative results, 100 μl plating following serial dilutions of urine sample must be performed [9]. The main value of urine culture is to identify microorganisms, most often bacteria; indirect indicators of the presence of bacteria (for example, urinary nitrites) are much less valuable than urine culture [5].

The number of bacteria in urine has been considered relevant for the diagnosis of UTIs since the Sixties, when Kass developed the concept of significant bacteriuria (10^5 CFU/ml) opening up to quantitative microbiology for the diagnosis of infectious diseases; his notion is still generally used to help diagnosis. Nevertheless, it has recently become clear that no fixed bacterial count can be applied to all kinds of UTIs and all circumstances, and even low bacterial concentrations are considered clinically relevant considering specific clinical pictures, sampling protocols and patient's sex. The problem of counting low numbers must then be considered [2].

Along with pathogen identification, outlining its antimicrobial susceptibility profile is considered to be crucial to ensure an appropriate treatment [10]. Antimicrobial susceptibility testing is routinely performed using the Kirby-Bauer disk diffusion technique according to Clinical and Laboratory Standards Institute (CLSI) guidelines, meaning culturing bacteria from urine samples on agar plates in presence of disks containing selected antibiotics; interpretation of results requires the measurement of halos of inhibition around disks according to reference tables [11].

As with most bacterial infections, diagnosis of UTI depends on culturing the clinical sample in the clinical laboratory, and results are typically delayed of two to three days from sample acquisition [10]. This is due to the need for sample transport to the laboratory and the time required for bacteria to grow on culture media [10]. Thus, the standard method for UTI diagnosis is time consuming and logistically difficult [6].

Since the patient cannot remain untreated during this rather prolonged period before definitive diagnosis is obtained, physicians usually prescribe broad spectrum antibiotics prior to antibiogram results. This practice has many undesirable consequences in the short and long terms, such as treatment failure leading to spread or chronicization of infection, increased health care costs, and increased antibiotic resistance by a growing number of bacterial strains. Given these drawbacks, it is obvious that a rapid and accurate method of UTI diagnosis and bacterial antibiotic susceptibility assessment would offer significant health benefits [12].

The introduction of partial and complete automation in clinical diagnostic in the 2000s has allowed the management of large-scale sample volumes and workflows optimization still providing reliable results for both pathogen identification and antibiotic susceptibility testing [10, 13].

Large-scale systems, anyway, are expensive and require more dedicate space, equipment and more personnel competence, which makes them applicable to a large hospital setting, but are difficult to establish in a small hospital, or in a limited-resource setting (e.g., developing countries). These high-throughput culture-based instruments, moreover, remain relatively slow and are not amenable for point-of-care use [10].

The introduction of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) technology in microbiology has allowed rapid and reliable bacterial identification, featuring both high sensitivity and specificity, improving efficiency and saving consumables and labor [14, 15]. MALDI-TOF technique is usually coupled with culture of urine samples, to allow isolation of bacteria and therefore obtain pure cultures, which will undergo MALDI-TOF analysis after some sample treatment. Recently, extensive databases have been developed that include protein profiles of main microorganisms involved in infections; some studies have therefore investigated the possibility to apply MALDI-TOF analysis directly to urine samples, yielding promising results also when coupling such analysis with screening methods, such as automated microscopic urine sediment analysis [16, 17]. It must be considered, however, that such high-throughput technology has high installation and maintenance costs, and requires dedicated spaces, limiting its use in routine analyses to centralized laboratories. Moreover, the technique cannot currently identify two species of bacteria when present simultaneously, and cannot determine antibiotic susceptibility; thus, traditional culture of urine samples is still necessary [18].

Nevertheless, the occurrence of more than one bacterial strain in urine samples participating in the infection should not be overlooked. Polymicrobic infections are more often associated with catheterization and aging, reaching 10% incidence rates in the community and 30% in hospital setting among elderly people [19]. Bacterial strains recovered from polymicrobic infection show metabolic alterations and altered virulence traits, such as antibiotic resistance [19]. However, relationships between coinfecting strains are not yet fully understood [20], although some studies are exploiting such infections' mechanisms [21, 22]. As clinical laboratories tend to report cultures showing single or clearly predominant bacteria and will not routinely report occurrence of polymicrobic associations, unless significant numbers of each species are detected, quite a large portion of UTIs are not correctly diagnosed nor treated, threatening patient's safety [19, 23–25]. Therefore, an improvement of diagnosis and clinical pathways is needed in order to enhance not only detection of pathogens in urine, but also profiling the whole microflora and determining the antimicrobial susceptibility of individual components.

3. When a urine culture followed by antibiogram is needed

Even though the incidence of UTIs is higher in women [6], also related pathologies in men, such as epididymitis and prostatitis, may be caused by migration of pathogens from the urethra or

bladder, the most common pathogens isolated being *Chlamydia trachomatis*, Enterobacteriaceae (typically *E. coli*) and *Neisseria gonorrhoeae*. For this last species, to reach correct diagnosis and plan following treatment, culture of mid-stream urine should be performed, together with nucleic acid amplification test (NAAT) on first voided urine or Gram staining in order to specifically detect *Neisseria gonorrhoeae* or *Chlamydia trachomatis* [6, 26].

Urine culture is recommended to determine the presence or absence of clinically significant bacteriuria in patients prior to urological interventions (e.g., surgery) and the presence of bacteriuria is controlled by directed pre-operative treatment of the detected pathogen [2, 6].

Urine culture is considered a valuable tool during patients' follow-up: in women whose symptoms do not resolve or recur within 2–4 weeks after the completion of treatment, urine culture and antimicrobial susceptibility test should be performed and a new antibiotic regimen should be considered. Afterward, in patients who underwent antibiotic treatment, a follow-up with subsequent urine culture should verify the treatment efficacy [2]. Urine culture is also recommended in women who present with atypical symptoms, pregnant women and males with suspected UTI [2].

In case of complicated UTIs, a broader range of bacteria is expected to be involved (often within the Enterobacteriaceae family), and these are more likely to show antibiotic resistance. Moreover, patients with a complicated UTI are more prone to have recurrent infections (more than 3 episodes/year) [2, 8, 27, 28]. Therefore, the choice of a therapy for these conditions must be supported by urine culture and antimicrobial susceptibility testing to avoid ineffective antibiotics administration.

Urine culture is also required in pediatric settings, where UTIs are the most common infections in children and infants, together with upper respiratory and gastrointestinal ones, with 30% recurrence rate reported within a year after initial UTI [2, 29]. Diagnosing pediatric UTIs may be difficult, because of communication difficulties in describing symptoms and vagueness of signs in small children; therefore, the definitive diagnosis of infection in children requires a positive urine culture [2].

In febrile patients with negative results on dipstick, microscopic, or automated urinalysis, urine culture is unnecessary if there is an alternative cause of the fever or inflammatory signs. However, if the dipstick and/or urinalysis are positive, confirmation of UTI by urine culture is mandatory [29]. In febrile children with signs of UTI (clinical signs, positive dipstick and/or positive microscopy, better if urine culture is available), antibiotic treatment should be initiated as soon as possible to eradicate the infection, prevent bacteremia, improve clinical outcome, diminish the likelihood of renal involvement during the acute phase of infection, and reduce the risk of immediate and long-term complications, including renal scarring and renal failure [29, 30].

4. Empirical treatment of UTIs

The gold standard for diagnosis and successful management of UTIs is to obtain identification and quantification of the infecting agents, along with antibiotic susceptibility assessment to

direct a specific therapy [31]. The use of microbiological culture method is well established in the diagnosis of infectious diseases [32]; however, such reference method is time-consuming, requiring on average 24–48hours, thus laboratory results are not immediately available, especially at patient's presentation in the Emergency Department [32, 33]. For this reason, in order to avoid even serious complications (e.g., sepsis) and mitigate patients' discomfort, the initial treatment specified by international guidelines as first step in UTIs management is most often empirical [32]. Nevertheless, this empirical approach contributes to mis- and overuse of antibiotics [10], resulting from unnecessary or inappropriate antimicrobial therapy, participating in recent arise in bacterial resistance. In fact, for people with symptoms of UTI and bacteriuria the main aim of treatment is relief of symptoms, but in case of unsuccessful treatment it could cause some alteration of urinary tract microflora, leading to an increased risk of clinical adverse events, including infections with multi-drug-resistant organisms and the development of antibiotic-resistant UTIs [1]. Infections caused by multi-drug-resistant pathogens, such as extended-spectrum beta-lactamase (ESBL) and carbapenemase producing Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and bacteria resistant to broad-spectrum antibiotics, such as fluoroquinolones and cephalosporins, are indeed increasingly recorded among UTIs and are the cause of a serious challenge to the public health system today [2, 10, 34].

The spread of antibiotic resistance is a threat to patients undergoing urological surgery in general [2], and multi-drug-resistant bacterial infections can limit the availability of effective treatment options, especially in low-income countries, rendering some UTIs difficult to treat and increasing healthcare costs [30].

This situation is generally promoted by several factors, including the overuse and misuse of antimicrobials in human and veterinary medicine and, indirectly, in agriculture. Measures to prevent and control the increase of antimicrobial resistance as well as the dissemination of resistance genes are crucial [35]. Prudent prescribing and rational use of antibiotics is a key component of action plans for reducing antimicrobial resistance [1, 2, 35, 36]. Antimicrobial stewardship programs have become a priority to optimize the outcome of prevention and treatment of infection while limiting overuse and misuse of antimicrobial agents [6], also following a systematic audit approach [37, 38]. In addition, non-antibiotic strategies are being explored [6]. There are many non-antimicrobial measures recommended, especially for recurrent UTIs [2, 28, 39, 40], but only a few results from well-designed studies are available for evidence-based recommendations [2, 41].

In general, the choice of antibiotics should be based, among other factors, upon identification and susceptibility pattern of the organism causing the UTI and the ecological collateral effects including selection of resistant bacteria by the chosen antimicrobial [2].

It must be considered, though, that the in vitro susceptibility of community-acquired uropathogens varies according to age and geographic region, and, as magnitude and variability of antimicrobial resistance patterns in the community grow, so does the need for continuous large-scale surveillance systems, in order to create databases linking epidemiological, clinical and laboratory data [42].

Therefore, the development and implementation of new clinical tools in routine medical practice could help optimizing antibiotic administration, leading to a more prudent and rational use of antibiotics. A rapid screen may be a more practical approach to yield benefits for the patient, the physician, and the laboratory [43].

The advent of new innovative diagnostic devices for UTI management, complementary to the reference culture-based methods, may lead to a new deal improving routine practice. Immunocompromised patients (e.g., diabetes mellitus, chronic kidney disease, and kidney transplant) with UTIs could particularly benefit from such diagnostic improvements. Clinical diagnosis of UTIs in this category of patients is challenging, because causative pathogens may be slightly different to those in the general population, and because of patients' clinical picture complexity. Early diagnosis is imperative in this group, and treatment of UTIs should be tailored according to individual patient characteristics [44].

5. Alternative and non-culture-based methods for the detection of UTIs

Because of the clinical importance of early UTI diagnosis, alternative rapid near-patient urine tests have been developed, such as urine dipsticks, which are widely used [31] in spite of their uncertain diagnostic accuracy [6]. The urine dipsticks test is commonly used for presumptive diagnosis of UTIs: it detects the presence of biochemical markers in urine samples which may be useful to establish the diagnosis of UTI [2]. Although many urine biomarkers for UTIs have recently been considered [45], markers that showed best results in diagnostic accuracy are nitrite and leukocyte esterase [6]. Although being cost-effective [46], such test shows low sensitivity that limits its clinical usefulness, [6] and analysis may be biased since a number of bacterial species are unreactive in these tests (e.g., no reduction of nitrates) [47, 48]. Furthermore, urine dipstick test does not detect bacteria, nor their concentration, which is essential to diagnose UTIs according to guidelines, and provides no information about antimicrobial susceptibility. Urine dipsticks are, anyway, cheap, easy to use, can be performed at doctor's office, in pharmacies or at home (even though urine dipstick test is not intended for self-diagnosis purposes [49], are available without prescription and provide results of easy interpretation within minutes.

Among hospital tests routinely used for urine analysis, microscopy examination of urine sediment has since long time been used, also undergoing automation to improve results. Although sensitivity is high, specificity is too low for exclusive use in clinical settings. Moreover, such technique requires sample centrifugation, and experienced personnel is needed to avoid errors in microscopic examination [6].

Flow cytometry found applications in many fields, also including medical disciplines [50]. Automated platforms of urinary flow cytometry have been widely adopted by centralized laboratories [10]. Flow cytometry allows of rapid detection of bacteria, white blood cells, red blood cells, epithelial cells, casts, crystals, yeasts and spermatozoa. They offer the benefit of standardize urine sediment analysis and reduce the error associated with subjective interpretation of results [51]. Nevertheless, the poor quality of available studies was confirmed in a

recent meta-analysis, which also showed current low accuracy and specificity of such method that should not be used as the sole screening tool for UTIs ([51], and references therein).

Dipslide technology has been proposed to simplify traditional culture-based methods: the test allows the detection of bacteria in liquid matrices by observing growth on different agar media (e.g., CLED agar and MacConkey agar) after immersion into sample and following 24-hour incubation. Overall, despite being simple to use and cost-effective, dipslide technology can only be considered as a guide to support further analyses: such test shows low accuracy when compared to the reference culture method [6], and no reliable detection of $<10^4$ CFU/ml can be obtained [7]. For this reason, dipslides are currently unsuited to routine use in clinical setting with further studies required to determine the best combination of culture media [6].

For the short term, molecular biology techniques such as real-time PCR could be used to complement conventional culture-based methods for pathogens identification, especially with regard to shortening the time to obtain results, shortening the time to decision of antibiotic therapy [32]. However, this method is limited by the broadness of the panel of pathogens included in the test, and both sensibility and specificity are low when compared to urine culture. Moreover, such technology requires many steps for sample preparation and does not allow a viable count, also considering that up to now the clearance of bacterial DNA from urine is unclear. The need for quantification in UTI diagnosis should drive future developments of commercial real-time PCR pathogen detection tools to include a quantification option [32].

In addition, possible new routes have been explored aiming to develop new clinical tools to help rapidly identify uropathogens, such as: the detection of volatile organic compounds in urine by gas chromatography and mass spectrometry and following comparison between profiles using compounds databases [52]; the use of Raman and Surface Enhanced Raman Spectroscopy, which can provide quantification and identification of bacteria populations and possibly assessment of antibiotic susceptibility, although results are still preliminary and must be significantly expanded [12]; the use of impedance spectroscopy to detect ultra-low concentrations of *E. coli* in human urine and provide quantification for UTI diagnosis [53].

Although rapid, these technologies do not provide microbiological diagnosis nor susceptibility information, which remain the cornerstone of diagnosis, particularly in settings of complicated UTI [10].

In summary, laboratory urine culture remains the gold standard investigation for UTI diagnosis [6].

6. The importance of point-of-care tests in UTI diagnosis

Some tests have been developed aiming to provide rapid and accurate diagnostic information to direct treatment decisions at the patient's bedside, which seem to have yielded good consent among practitioners [54].

Rapid and definitive near-the-patient diagnosis of UTI would have a favorable impact on its management [10]: a rapid turnaround of results could influence clinical decisions such as triage, referral, and decision to discharge the patient. Prompt clinical interventions could be provided by caregivers, meaning timely antibiotic treatment could be initiated and imprecise empirical treatment avoided [10, 55]. This would improve health outcome also providing diagnostics tools for limited-resource settings [55]. Point-of-care tests (POCTs) can provide considerable savings in health care costs by reducing the number of patients visiting health centers simultaneously improving the quality of life for patients by reducing their number of visits to health care facilities [55]. An early diagnosis based on POCTs can also enable clinicians to start antibiotic administration earlier and thereby increase chances of successfully treating the disease. In future, innovation through rapid and reliable POCTs is advisable, updating technologies to ensure efficient data management and simplify use by healthcare professionals, eventually lowering medical costs [55]. POCTs could allow a better screening and follow-up of patients not only by hospitals, but also by pharmacies and general practitioners, helping decentralize diagnosis and therefore reduce the workload of laboratories, with consequent reduction of costs related to urine analysis and management of UTIs and reduction of human errors leading to mix-ups of patient samples sent to off-site laboratories [55].

Several POCT for UTIs have been developed and are currently commercially available. They can be distinguished in: (*i*) culture-based devices, (*ii*) (semi-)automated urine analyzers and (*iii*) enzymatic assays [56]. All culture-based devices allow semi-quantification of bacterial growth and evaluation of the infecting bacterial species. Most often, samples need to be cultured and appreciable bacterial growth can be achieved in not less than 16–24 hours. The (semi-)automated urine analyzers have the same read-out as the urine dipstick test and UTI diagnosis is based on the presence of markers such as nitrites and leukocytes. Although the human error involved in visual interpretation can be eliminated and results can be obtained in 1–2 minutes, these tests do not significantly improve current practice exhibiting very low sensitivity and limited positive predictive value. The same problem has been reported for enzymatic assays [57–61].

Biosensors offer a promising approach for improving molecular diagnostic in POC settings [10]. Biosensors are binary systems composed of a recognition and a transducer element that can generate a measurable proportional signal following binding of the target analyte to the recognition element (e.g., antibody, enzyme), which allows quantitative detection of a biological entity [10]. Even though biosensors technology has been applied successfully to the field of clinical diagnostic (e.g., blood glucose and pregnancy tests), no such tests have been implemented to date to improve routine diagnosis of UTIs [55]. Indeed, key features of biosensors, such as portability, rapidity, and cost-effectiveness in comparison with their macro-scale counterparts, could be crucial for the development of a POCT for UTI pathogens identification and antimicrobial susceptibility assessment. Nevertheless, considering the urine matrix, such biosensors would require multistep sample preparation with amplification/enrichment steps to improve target detection, and such biological matrix could impair sensor performance with its variations in biochemical parameters (e.g., inhibitors, non-specific binding). Moreover, such tests should have a multiplex approach to ensure identification of a broad

panel of pathogens in different clinical scenarios, and should provide antimicrobial susceptibility testing to drive treatment, but genetic non-culture based approaches are limited by the fast evolution rate of defense mechanisms among bacteria. Biosensors POCTs could anyway complement reference methods helping saving resources in terms of materials, money and time, because rapid, simple and cost-effective tests could optimize further analyses therefore reducing the burden on laboratories [10].

The Micro Biological Survey (MBS) POCT "UTI CHECK" appears to hold good promise for early detection and antimicrobial susceptibility profiling of uropathogens. The MBS method allows rapid and accurate bacterial quantification through an automated colorimetric culture-based test; urine samples are inoculated into disposable ready-to-use reaction vials, which color will change thanks to redox indicators following bacterial growth after incubation (see **Figure 1**). Results of preliminary *in vitro* validation studies [62, 63] showed that the results obtained with this method are comparable to the reference culture-based methods.

Such findings encouraged further research in hospital settings, and clinical trials have been carried out [31] in which the efficacy of the MBS POCT was compared to the reference method, used in hospital routine, and other methods, such as urine dipsticks: the MBS POCT

Figure 1. MBS "UTI CHECK." MBS "UTI CHECK" is an automated colorimetric culture-based test. It is composed by mono-use, disposable and ready-to-use reaction vials (right) in which 1 ml of urine can be inoculated without any preliminary treatment. Up to eight urine-inoculated reaction vials can be independently allocated in an automatic thermostated optical reader (left) that it is able to detect color change induced by the growth of bacteria and automatically correlates the time required for color change with the number of bacteria present in the urine samples. Different vials contain selected antibiotics and the occurrence of the color change in the presence of antibiotics indicates antibiotic resistance of bacteria present into the urine sample.

Product	Manufacturer/ location	Description of device	Analysis time	Additional equipment required	Positive result outcomes	Method principle	Number of samples tested; Test population	Threshold for significant growth	Accuracy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Ref
FLEXICULT™	Statens Serum Institut Diagnostica/ Denmark	Chromogenic agar plate with 6 segments – 5 evaluating anti-biotic sensitivities and 1 control segment	24 hours	Incubator	Semi-quantification of bacterial growth, evaluation of the species present, and assessment of sensitivity to the antibiotics in each of the plate segments	Microbial culture and susceptibility testing	N = 200/124 (outpatient setting)/76 (secondary care setting)	$\geq 10^5$ CFU/ml	—	87.0% (67.9–95.5)	83.2% (74.7–89.2)	[23]
Uricult Trio	Orion Diagnostics/ Finland	Plastic slide with two opposing agar media	16–24 hours when incubated at 36.8 °C or 1–3 days at room temperature	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Microbial culture	198 (pediatric patients aged 0–7)	$\geq 10^4$ CFU/ml	—	68%	82%	[26]
							434 (primary health care setting)	$\geq 10^3$ to $\geq 10^5$ CFU/ml for doubtful uropathogens	88%	88%	90%	[27]
DipStreak (Chromostreak)	Novamed/ Israel	Plastic paddle with two opposing agar media, housed in a closed transparent plastic tube	18–24 hours	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Microbial culture	N = 1070 (251 hospitalized patients and 819 outpatients)	$>10^5$ CFU/ml (single organism + mixed culture)	98%	95.7%	99.2%	[28]

Product	Manufacturer/ location	Description of device	Analysis time	Additional equipment required	Positive result outcomes	Method principle	Number of samples tested; Test population	Threshold for significant growth	Accuracy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Ref
DiaSlide	Novamed/ Israel	Hinged plastic case containing two opposing agar media	24 hours	Incubator	Semi-quantification of bacterial growth	Microbial culture	473 (prescreened hospital urine specimens using UriScreen)	$\geq 10^4$ CFU/ml	—	98.3%	97.5%	[29]
onSite	Trek Diagnostics System/USA	Hinged plastic case containing two opposing agar media	Not specified	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Microbial culture						
MBS UTI CHECK	MBS srl/Italy	Mono-use disposable vials for chromogenic analysis	3–5 hours	MBS Multireader	Semi-quantification of bacterial load, assessment of sensitivity to selected antibiotics	Measure of the catalytic activity of redox enzymes of bacteria	N = 223 (emergency department)	$\geq 10^5$ CFU/ml (single organism + mixed culture)	99%	92.6% (75.7–99.1)	100% (94.9–100)	[17]

Table 1. Features of main POCTs for UTI diagnosis.

showed high accuracy, sensitivity and specificity, comparable to the reference method's and higher than urine dipsticks' [31]. Although not providing bacterial identification, MBS "UTI CHECK" allows bacteria detection and quantification in urine samples. Preliminary results showed that this POCT can provide uropathogens' susceptibility pattern to a panel of antibiotics. The analytical time required for UTI diagnosis is usually less than 3 hours (up to 5–6 hours when the bacterial load is equal or less than 1×10^5 CFU/ml) and antimicrobial susceptibility assessment is obtained in less than 10 hours, which could guide downstream medical decisions with crucial information within few hours. Notably, this method features cost-effectiveness, user-friendliness, portability, easy interpretation of results, which all can lead to successful use at the patient's bedside [31]. The MBS point-of-care testing device could be developed into a valuable aid for the management of UTIs, possibly addressing more precise diagnosis and appropriate therapy also proving useful in treatment outcome evaluation. Features of main POCTs available on market, including MBS "UTI CHECK," are summarized in **Table 1**.

7. Conclusions

To date, hospital settings rely mainly on laboratory analysis following urine culture reference method; this approach requires a considerable effort in terms of workload and up to 3 days to achieve results. Furthermore, it can lead to unnecessary antimicrobial overuse which ultimately promotes the emergence of resistance [31].

The unnecessary use of antibiotic treatment may be minimized following two roads: on one hand by the establishment of antibiotic stewardship programs which require healthcare staff involvement in regular training in best use of antimicrobial agents for an improved adherence to local, national or international guidelines and regular consultation with infectious diseases physicians, with audit [6]; on the other hand by improving diagnostic pathways [1], possibly relying on use of POCTs that feature incorporation of pathogen identification with antimicrobial susceptibility testing, sufficiently versatile to be adaptable for different pathogen profiles in different clinical scenarios [10]. The advent of accurate and robust POCTs could allow a more rational screening before treatment or admission and to improve follow-up of patients for treatment outcome evaluation and for monitoring of antimicrobial prescribing performance and local pathogen resistance profiles [6].

Such approach could ultimately lead to treatment customization according to individual patients' characteristics through fast antibiotic susceptibility testing results [44], with the ultimate aim of improving patients' welfare and reduce healthcare costs.

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Chapter 3

Urinary Tract Infections in Renal Transplant Recipients

Justyna Gołębiewska and Alicja Dębska-Ślizień

Additional information is available at the end of the chapter

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Abstract

Renal transplantation (RTx) is the treatment-of-choice for a significant number of patients with end-stage renal disease. Despite recent accomplishments, both surgical and medical complications still exist. Urinary tract infection (UTI) is the most common infectious complication after RTx, while asymptomatic bacteriuria is the most common manifestation of bacteriuria. UTI can impair graft function, potentially reducing graft and patient survival. The aetiology changes with time after RTx. The epidemiology of most of these infections is also changing with resistant organisms being isolated more often than in the past. Several factors increase the risk of infection in RTx patients, and the presence of multiple risk factors in the same patient is not uncommon. These include immunosuppression, urinary flow impairment (most often caused by stenosis or strictures at the vesicoureteral junction, benign prostate hypertrophy or vesicoureteral reflux), and treatment-related factors such as the use of catheters and double-J stents. Early diagnosis and effective treatment are key elements in salvaging both the allograft and the patient. This chapter reviews the definitions, epidemiology, microbiology, screening, clinical manifestations, diagnosis, impact on renal allograft function, evaluation after diagnosis, treatment, prevention including long-term prophylaxis, and the unique challenges of diagnosing and managing recurrent bacterial UTIs in a RTx care setting.

Keywords: urinary tract infections, renal transplantation, treatment, prevention, renal allograft function

1. Introduction

Kidney transplantation is the renal replacement therapy of choice for the constantly increasing number of patients with end-stage renal disease (ESRD). The huge headway in immunosuppressive treatment has resulted in improved renal graft survival rates, at the same time making infectious complications an even more common problem in the

renal transplant (RTx) population, with the urinary tract being the most prevalent infection site. Apart from immunodeficiency resulting from the use of immunosuppressive drugs, RTx patients often suffer from numerous urological malformations, vesicoureteral reflux (VUR) that is a permanent symptom after RTx, and are exposed to invasive diagnostic and therapeutic procedures involving the urinary tract. That is why urinary tract infections (UTIs) are the most common infectious complication among RTx recipients with up to 60% prevalence during the first year post-transplant [1, 2]. UTIs are important not only because of the scale of the problem but due to their potential negative influence on graft and RTx recipients' outcomes.

2. Epidemiology

Urinary tract infections (UTIs) are major causes of morbidity and hospitalization in renal transplant recipients. Infections, with the urinary tract as a major site, are the most common cause of acute kidney allograft injury, and prevalence of UTI-associated acute kidney injury far outnumbers episodes of acute rejection and calcineurin inhibitor toxicity [3].

There is a wide variation in the reported incidence of UTIs, most likely associated with differences in the definition of UTI, length of follow-up and variation in the use of post-transplant antibiotic prophylaxis. In a recently published meta-analysis on the prevalence and predictive factors of UTI in patients undergoing renal transplantation that included 13 studies with a total of 3364 patients evaluated, 1033 (30.71%) had UTIs [4]. The included studies provided different estimates of prevalence, which ranged from 16.0 to 75.0%, and the pooled prevalence of UTIs was 38% (95% CI, 29–47%; $p < 0.01$). Of note, RTx recipients followed for 1–2 years had significantly higher prevalence than those followed for 2–5 years (34 vs. 43%).

3. Definitions

All UTIs can be classified into one of the four following categories:

(1) Asymptomatic bacteriuria (AB), defined as isolation of bacterial strain in quantitative counts ≥105 CFU in a clean-catch voided urine specimen in the absence of any symptoms of lower or upper UTI or $<10^5$ CFU in patients treated with antibiotics or $\geq 10^3$ CFU in a single catheterized urine specimen, irrespective of the presence of leukocyturia.

(2) Lower UTI, which is the presence of bacteriuria and clinical manifestations of dysuria, frequency or urinary urgency and fever <38°C in the absence of acute graft pyelonephritis (AGPN) criteria.

(3) Upper UTI (AGPN), defined by the presence of significant bacteriuria, fever >38°C and/or graft pain and/or acute graft function impairment.

(4) Urosepsis—life-threatening organ dysfunction caused by a dysregulated host response to the upper UTI.

Recurrent infections are defined as 3 or more episodes of symptomatic UTIs over a 12-month period or 2 episodes in the previous 6 months and can be divided into:

(1) Relapses: defined as the isolation of the same microorganism that caused the preceding infection in a urine culture obtained ≥2 weeks after finishing the previous treatment. The isolation of the same microorganism that caused the preceding infection in a urine culture obtained <2 weeks after finishing the previous treatment should be considered a treatment failure.

(2) Reinfections: defined by a new episode of UTI with the isolation of an agent other than the one that caused the previous infection.

Definitions of multidrug-resistant (MDR) bacterial infections:

(1) Criteria for multidrug-resistant (MDR) bacteria: non-susceptible to ≥1 agent in ≥3 antimicrobial categories or methicillin resistance in the case of *S. aureus*.

(2) Criteria for extensively drug-resistant (XDR) bacteria: non-susceptible to ≥1 agent in all but ≤2 categories (i.e. bacterial isolates remain susceptible to only one or two categories).

(3) Criteria for pan drug-resistant (PDR) bacteria: non-susceptible to all the antimicrobials.

(4) Heteroresistance is defined as the presence of mixed populations of drug-resistant and drug-sensitive cells in a single clinical specimen.

4. Predisposing factors for UTIs after RTx

Many factors are believed to contribute to the high incidence of UTI in RTx recipients. Some exist prior to transplant, including female gender, diabetes mellitus and underlying urinary tract abnormalities. Peri-transplant factors are often related to instrumentation of the urinary tract, including ureteral stenting and prolonged urinary catheterization. Additional risk factors contributing to UTI post-transplant include immunosuppression and graft dysfunction or rejection. It is noteworthy that so far no direct association has been found between the risk of UTI and dose or type of maintenance immunosuppression. It is the net state of immunosuppression that impairs host defense capability against infections in general. Various authors have suggested different potential UTI risk factors, and their findings are not always consistent. The potential pre-, peri- and post-transplant risk factors for UTI in RTx recipients are shown in **Table 1**.

Of note, significant urine flow impairment, both existing pre-transplant or appearing post-transplant, seems to be of major importance. The bladder outlet obstruction, particularly in

Pre-transplant	Peri-transplant	Post-transplant
Urine flow impairment	Ureteral stents	Urine flow impairment
Female gender	Bladder instrumentation	• Vesicoureteral reflux (VUR)
Diabetes	Deceased-donor grafts	• Strictures at the uretero-vesical junction
Urinary tract anomalies	Double kidney transplants	• Benign prostate hyperplasia
Glomerulonephritis		Immunosuppression
		Acute rejection
		Reduced graft function

Table 1. Risk factors for UTI in renal transplant recipients.

males, may not be appreciated until after the transplant, leading to prolonged instrumentation and an increased risk of UTI. The likelihood of AGPN development is 20-fold higher in patients with vesicoureteral reflux (VUR) or strictures at the uretero-vesical junction or benign prostate hyperplasia (BPH). Active reflux has long been reported as being significantly associated with poor graft outcome [5]. In a study by Dupont et al., VUR was found in almost half of RTx patients with recurrent UTIs, and patients with VUR were more prone to develop renal scarring than those without VUR [6]. On the other hand, in a recent study by Margreiter et al., 40% of 646 consecutive RTx recipients were diagnosed with VUR by voiding cystourethrography, and VUR did not affect the occurrence of UTIs. Simple UTI was diagnosed in 24.7% of patients with VUR and 27.2% of patients without VUR ($p = 0.78$). Recurrent UTIs were noted in 4.2% (with VUR) versus 3.9% (without VUR) of the enrolled patients ($p = 0.67$). However, the authors did not analyze the incidence of UTI according to VUR grade [7]. In a retrospective cohort of 23,622 adult male primary RTx recipients, also benign prostate hyperplasia was independently associated with recurrent UTI [8]. Considering the significant influence of urinary flow abnormalities on the likelihood of AGPN development, we would strongly recommend examination for VUR or urine flow obstruction even at the first AGPN episode.

5. Impact on renal allograft function

The reports on the influence of UTIs on long-term kidney allograft function are inconsistent. The true impact of the whole spectrum of clinical manifestations of UTIs, on patient and graft outcome, so far has not been established. The general assumption is that asymptomatic bacteriuria (AB) is benign, as opposed to acute graft pyelonephritis or urosepsis. Still, the paucity of symptoms might be attributable to immunosuppression with actual ongoing inflammation of unrecognized significance. In one small study, kidney transplant patients with asymptomatic bacteriuria had elevated urine IL-8 level; and the authors hypothesized that this phenomenon may reflect an impaired immune response to bacterial infection and occult inflammatory process in the urinary tract [9]. Pellé et al. showed that acute graft pyelonephritis (AGPN) was

an independent risk factor for the decline in renal function in a group of 172 RTx recipients [10]. Also a more recent study analyzing the effects of recurrent UTIs on graft and patient outcomes, in a population of 2469 RTx recipients, showed both poorer graft and patient survival in patients with a history of ≥3 UTIs in any 12-month period or ≥2 UTIs in any 6-month period, irrespective of the causative organism [11]. However other reports did not confirm this relationship. Not only asymptomatic bacteriuria but also AGPN did not affect long-term renal graft function prognosis [12–15]. However, even if UTIs do not influence graft survival directly, they can pose a significant risk indirectly by leading to bacteraemia, acute rejection or cytomegalovirus (CMV) infection.

6. Aetiology and timing of infections

UTI after kidney transplantation is most often caused by Gram-negative organisms (around 50–90%), with *Escherichia coli* as the most frequently isolated microorganism in urine cultures, similarly to general population. However, aetiology differs between the early and late periods after RTx [16]. *Enterococcus* species has emerged as an important pathogen and now

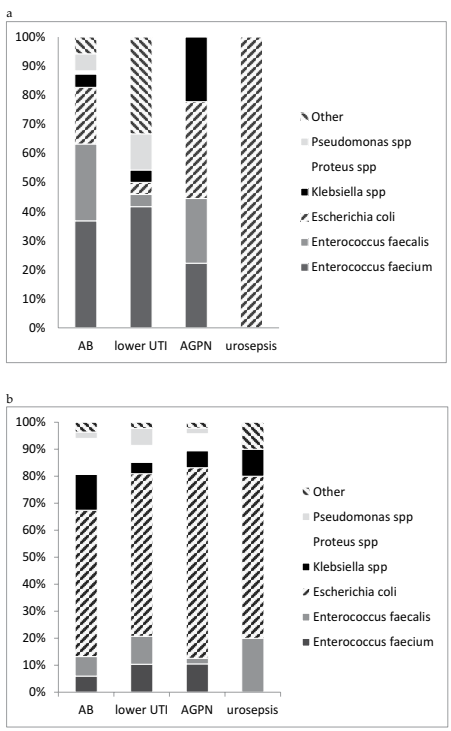

Figure 1. Proportion of different causative agents according to the type of UTI (a) during the first month post-transplant and (b) during 2–12 months post-transplant [16].

accounts for up to 30% of UTIs, especially in the first post-transplant month. In a study by Alangaden et al. *Enterococcus* spp. accounted for 33% of UTIs, but authors failed to identify any specific risk factor associated with the predominance of this uropathogen [17]. Also in a study by Bonkat et al., *Enterococcus* spp. were bacteria most commonly responsible for microbial ureteral stent colonization in RTx recipients. The authors found two possible explanations for this phenomenon. *Enterococcus* spp. possess biofilm formation properties on various kinds of indwelling medical devices; and routine urine cultures often fail to identify biofilm forming Gram-positive pathogens, unlike the sonication technique used in that study to dislodge adherent microorganisms [18]. Another possible explanation of a high number of *Enterococcus* spp. infections is the routine use of cephalosporins in perioperative prophylaxis. This antibiotic acts against Gram-negative *Bacilli*, therefore it promotes selection of *Enterococcus* spp.

Beginning from the second month, *Escherichia coli* is the most frequently isolated causative agent, followed by *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp. and *Pseudomonas* spp. (**Figure 1**).

7. Multidrug-resistant bacteria

With the widespread use of antibiotics, including the routine use of antimicrobial prophylaxis in RTx recipients, the prevalence of multidrug resistance (MDR) among uropathogenic bacteria is increasing, irrespectively of region and country. The most widely accepted definition of MDR includes lack of susceptibility to one or more agents in three or more antimicrobial categories active against the isolated bacteria. Of note, also extensively drug-resistant (XDR) and pan drug-resistant (PDR) strains have been identified.

In patients receiving trimethoprim-sulfamethoxazole prophylaxis, over 60% of UTIs have been reported as caused by trimethoprim-sulfamethoxazole-resistant organisms [19]. The treatment of AB has also been associated with antimicrobial resistance. In a study of patients with asymptomatic *E. coli* or *E. faecalis* bacteriuria, treatment led to selection of resistant organisms in almost 80% of treated cases [20]. The emergence of ESBL-producing, or carbapenemase-producing, organism pathogens has been the most important threat in nosocomial infections in recent years [21]. Although antibiotic resistance has been a concern since the introduction of penicillin, the past two decades have seen a marked increase in resistance, especially related to beta-lactams. Resistance in Gram-negative pathogens continues to increase, with multidrug resistance in the *Enterobacteriaceae* becoming one of the most important crises faced by the medical community. A major contributing factor is the acquisition of large plasmids that can encode resistance factors for multiple drug classes. As seen from the recent literature, organisms such as *E. coli* and the *Klebsiella* are acquiring more diverse integrons and transposons that are included in a multiplicity of transferable plasmids capable of encoding every class of beta-lactamase.

It seems that immunosuppression may influence the resistance of enterococcal spp. to β-lactam-based antibiotics by affecting the expression of the penicillin-binding proteins (PBPs). In enterococcal strains isolated from RTx patients, the expression of the PBP5 gene was higher than in

commensal strains. As cyclosporine seemed to promote higher expression of PBP5 than tacrolimus, β-lactam antibiotics may be more effective when tacrolimus-based immunosuppression protocols are implemented [22].

In a recently published study analyzing recurrent UTIs in a cohort of 2469 RTx recipients, the authors found pronounced differences in antimicrobial resistance patterns between non-recurrent and recurrent UTIs [11]. Isolates from the cases of recurrent UTIs were more likely to be resistant to first- and third-generation cephalosporins, trimethoprim-sulfamethoxazole, nitrofurantoin and fluoroquinolones, to extended-spectrum b-lactams and aminoglycosides.

In a retrospective case series by Winters et al., 85% of solid-organ transplant recipients diagnosed with infection due to ESBL-producing bacteria received inadequate empiric therapy [23]. This means that all RTx recipients with a history of UTI due to ESBL-producing Gram-negative pathogens, presenting with symptoms of a new UTI, should receive an empiric therapy with a carbapenem until a urine culture result with susceptibility profile is available.

8. Diagnosis

UTIs in RTx recipients may either be asymptomatic or have an atypical clinical presentation. Therefore the diagnosis based solely on clinical grounds may be of questionable accuracy. What is more, every symptomatic, either lower or upper UTI in any transplant recipient, is considered complicated: as it is associated with structural and functional abnormalities of the genitourinary tract and immunocompromised status that increases the risk for acquiring an infection or of failing therapy. For this reason urine cultures should be obtained in every single case, in order to base therapy upon susceptibility pattern determinations.

9. Asymptomatic bacteriuria

Asymptomatic bacteriuria is a frequent finding in kidney allograft recipients, with almost 40% incidence [16]. So far there are no evidence-based recommendations for screening and treatment of AB in renal transplant recipients, because sufficient data is lacking [24]. The American Society of Transplantation Infectious Diseases Guidelines recommend limiting screening to the first post-transplant month, but these recommendations are mostly expert opinion [25]. Fiorante et al. showed that the incidence of AGPN was significantly higher in patients with a history of multiple episodes of AB than in patients without, despite or due to the provided antibiotic treatment [26].

Patients with no episodes of AB seem to develop significantly fewer symptomatic infections than patients with a history of recurrent AB. As reinfections seem to outnumber relapses and only a very few episodes of symptomatic UTIs are preceded by AB with the same causative agent in patients with a history of recurrent AB, it seems that AB is more of a marker of increased susceptibility to infections, not a direct risk factor [16]. This is in agreement with the findings from a non-transplant population of young women, where the treatment of AB in patients affected by recurrent UTI was associated with a higher rate of symptomatic UTI [27].

The authors hypothesized that this phenomenon resulted from ecological effects of antibacterial agents on the human microflora. However, Rice et al. found an association between AB progression to systemic infection with acute kidney allograft injury and a unique pattern of adherence factors that is P fimbriae but not Dr. fimbriae expression [28]. So, AB might be an actual risk factor for symptomatic UTIs depending on the virulence of uropathogens.

A number of studies attempted to elucidate if the treatment of AB in RTx patients is in fact helpful or harmful in preventing symptomatic infections [19, 20]. One retrospective observational study included a total of 112 patients with AB. The decision as to whether, or not, to treat AB was made by the attending physician. The primary outcome, defined as hospitalization for symptomatic UTI or a 25% decline in the eGFR, occurred more frequently among patients treated with antibiotics. However, the authors called attention to the fact that those treated patients may have initially been at higher risk for adverse outcomes, thus masking the benefit of the treatment [19]. Another retrospective study included 77 RTx recipients who developed 334 AB episodes later than 1-month post transplantation. AB episodes were classified into four groups depending on the presence of pyuria and grade of bacteriuria. Spontaneous bacterial clearance occurred in 59% of untreated episodes. The resolution of bacteriuria was not more frequent in treated, as compared to untreated, episodes. However, antibiotic treatment in patients with high-grade bacteriuria and concurrent pyuria resulted more frequently in negative control cultures than untreated episodes. The authors concluded that a watch-and-wait strategy for bacteriuria in the absence of pyuria might be safe in the RTx population [20]. In 2016, the results of a randomized controlled study were published. Systematic screening and treatment of AB beyond the second month after transplantation provided no apparent benefit among KT recipients when the occurrence of acute pyelonephritis at 24-month follow-up was considered. The treatment also did not affect the secondary outcomes, which included lower UTI, acute rejection, *Clostridium* difficile infection, colonization or infection by multidrug-resistant bacteria, graft function and all-cause mortality [29].

10. Treatment

Selection of initial empiric treatment should be based on local epidemiological data and the patient's history of resistant organisms. Once susceptibility data are available, the initial therapy should be deescalated, so that the most narrow-spectrum antibiotic is used to complete the course of therapy. Care should be taken to avoid treating asymptomatic patients, in order to reduce the possibility of infection with MDR pathogens.

Lower UTIs require minimum 7-day therapy with an effective agent while upper UTIs at least 2–3 weeks. The resolution of infection should be demonstrated before the cessation of treatment. Stents or catheters may be covered with bacterial biofilm, so their removal is generally required for resolution of UTI. For empirical treatment of suspected bacterial infections in RTx patients, the selection of antimicrobial agents should be based on local epidemiological data and on the patient's history of colonization or infection with antibiotic-resistant organisms.

There is no evidence to support the use of combination antibiotic therapy for the treatment of ESBL, but in haemodynamically unstable or critically ill patients, adding an aminoglycoside to carbapenem seems a reasonable strategy. Amoxicillin-clavulanate and fosfomycin showed a clinical efficacy of 84 and 93%, respectively, in the treatment of cystitis caused by ESBL-producing *E. coli* but only when the isolate showed susceptibility to those drugs [30]. Other options in the case of proven susceptibility include tigecycline, cotrimoxazole, quinolones and nitrofurantoin.

The combination antibiotic therapy is a standard of care in carbapenemase-producing *Enterobacteriaceae* infections [31, 32]. Colistin is the most active agent against these strains and should be considered the basis of treatment in most patients [33]. The options for the use of combination antibiotic therapy include aminoglycosides, fosfomycin or even high-dose carbapenems [31, 32, 34]. Tigecycline could represent an optimal choice for patients with co-infection with additional MDR pathogens [e.g. vancomycin-resistant *Enterococci* (VRE) or methicillin-resistant *Staphylococcus aureus* (MRSA)].

In the case of severe infection with sepsis, the option of reduction/discontinuation of immunosuppression together with surgical/urological intervention should also be considered.

In severe upper UTIs and/or recurrent infections, imaging should always be obtained to rule out structural causes or persistent foci of infection. Ultrasound may confirm the presence of hydronephrosis. When there are no visible structural abnormalities on ultrasound, it may be necessary to perform fluoroscopic voiding cystourethrogram to diagnose severe vesicoureteral reflux (VUR), computed tomography urography to visualize the cause of urine flow obstruction or uroflowmetry to recognize the problem with delayed bladder emptying. In elderly RTx recipients, the aforementioned functional abnormalities may be secondary to benign prostate hyperplasia (BPH). Since most patients undergoing dialysis are oliguric or anuric, urinary obstruction due to BPH and related lower urinary tract symptoms become evident after RTx and restoration of diuresis. As opposed to native kidneys, the transplanted kidney's ureter is shorter, and there is no valve at the vesicoureteral junction preventing backflow, so low-grade BPH may cause symptoms that would not be present in a non-RTx patient. Medical therapy of BPH, both pharmacologic and surgical, such as transurethral resection of the prostate is safe and improves urinary flow and bladder emptying, to allow a significant and durable improvement of the kidney allograft function.

11. Prevention and prophylaxis

Appropriate attention should be given to the prevention of UTI with correction of structural abnormalities of the urinary tract in the potential RTx recipients prior to transplantation. Any type of voiding dysfunction should be considered and addressed.

In the immediate post-transplant period, vigilance for donor-transmitted infection is important, together with routine perioperative antibiotic prophylaxis recommended by the hospital's epidemiologist, taking into account current antibiotic resistance of Gram-negative strains. In the

case of a positive donor's or organ preservation fluid cultures, the antibiotic should be chosen according to susceptibility profiles. The use of indwelling urethral catheters and ureteral stents should be minimized.

Patients should be instructed to drink a lot of fluids and urinate frequently, without waiting for the urge to urinate.

There is no consensus regarding the optimal strategy and duration of recurrent UTI prophylaxis, so the decision to give it, or not, depends on the experience of the treating physician. Traditionally trimethoprim/sulfamethoxazole prophylaxis has been used as the prevention of both asymptomatic bacteriuria/UTI and Pneumocystis pneumonia after RTx. However, over the past few years, it has become less effective as uropathogens have become more resistant to this regimen. Of note, ESBL-producing *E. coli* are usually susceptible to nitrofurantoin, while most *Klebsiella* spp. strains are resistant to this antibiotic.

Several possibilities exist in an attempt to mitigate the damage caused by resistant pathogens. In the general population, there are ongoing attempts to use nonantibiotic strategies, such as cranberry products, D-mannose, probiotics, immunoactive prophylaxis with several types of vaccines, intravesical glycosaminoglycan replenishment therapy with the use of chondroitin sulfate and low molecular weight hyaluronic acid in the treatment and/or prevention of recurrent UTIs [35]. So far the use of all these products has not been extensively studied in RTx population, except for single-case reports on the use of cranberry products. Little information is also available about the usefulness of intestinal decolonization in RTx patients.

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Chapter 4

Urinary Tract Infection in Renal Allograft Recipents

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Additional information is available at the end of the chapter

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Abstract

Renal replacement therapy in the form of renal transplantation (RT) is the treatment of choice in these patients. Various factors influence the graft survival, infections being most common. Infections account for 16% of patient deaths and 7.7% of death censored graft failure in renal transplant patients. Urinary tract infection (UTI) is the most common infectious complication accounting for 45–72% of all infections. According to few studies UTI may have a negative impact over the long term survival of renal allograft. There are multiple factors that predispose these patients to UTI. Elderly age group, female gender, increased duration of catheterization and anatomical abnormalities of the urinary tract are most common predisposing factors. E. coli is the most frequently isolated organisms from the urine of these patients. We would proceed further with two cases which presented as UTI in post-transplant period. The first patient transplanted (living donor related) for diabetes induced end stage renal disease had developed UTI 4 years post-transplant. The other patient underwent deceased donor renal transplant for adult polycystic disease related chronic kidney disease, presented 2 years post-transplant with UTI.

Keywords: renal transplantation, urinary tract infection, renal allograft, graft function, immunosuppression

1. Introduction

Clinical information (Case 1): A 53-year-old male patient, with a history of arterial hypertension, type 2 diabetes mellitus, and renal failure, caused by diabetic nephropathy diagnosed 5 years back and was on maintenance hemodialysis. The patient underwent live donor renal transplantation in June 2013. The intraoperative and post-operative period was unremarkable

and he was put on Tacrolimus based immunosuppression thereafter consisting of Prednisone (20 mg/day), Mycophenolate sodium (360 mg/day), and Tacrolimus (1.5 mg/day level:4.6 ng/ml). He was on regular follow-up for routine urine examination, serum creatinine and serum electrolytes and hemogram. Nearly 4 years post-transplant he was admitted with complaints of low grade intermittent febrile episodes and painful micturition. There was slight rise in the serum creatinine levels to 2.4 mg/dL (baseline: 1.8 mg/dL). The urine output was however normal. Complete blood count performed revealed neutrophilic leukocytosis with total count of 14.2 × 10 ^{6}/μl, with predominance of neutrophils on differential, the absolute neutrophil count of 14 × 10 ^{6}/μl. Urine examination revealed urine albumin of +1 by dipstick method, pH of 5.0 and specific gravity of 1.020. **Clinical information (Case 2):** A 38-year-old female patient, underwent deceased donor renal transplantation for adult polycystic kidney disease induced chronic kidney disease. The intraoperative and post-operative period was unremarkable and she was on conventional Tacrolimus based immunosuppression thereafter consisting of Prednisone (20 mg/day), Mycophenolate sodium (360 mg/day), and Tacrolimus (1.5 mg/day; level:6.8 ng/dL). She was on regular monitoring for routine urine examination, renal function tests and complete blood counts. Nearly 2 years post-transplant she was admitted with complaints of intermittent high grade febrile episodes, pain in abdomen and nausea. The serum creatinine level at the time of presentation was found to be raised to 3.6 mg/dL (baseline: 1.2 mg/dL). The patient had normal urine output. Complete blood count performed revealed neutrophilic leukocytosis with total count of 18.6 × 10^{6}/μl, with predominance of neutrophils on differential, the absolute neutrophil count of 12 × 10^{6}/μl. Urine examination revealed urine albumin of +2 by dipstick method, pH of 4.6 and specific gravity of 1.040. **Summary**: So here we have two patients who underwent renal transplant for end stage renal disease and presented with signs and symptoms of urinary tract infection. Both the patients presented with rise in serum creatinine as well as pyuria on urine examination(not written in the text above)clinical suspicion of urinary tract infection. We would in further sections study how we proceeded with both the cases, investigations performed and management of both. In this brief review we would discuss the incidence of urinary tract infection in post-transplant patients, risk factors and how to manage a case with UTI.

1.1. Incidence of posttransplant urinary tract infections

Transplantation has become the gold standard treatment of end-stage disease in the present era. Of all the organs that are transplanted, kidneys remain the most frequently transplanted organ [1–5]. RT is regarded as an effective treatment for patients with advanced chronic renal disease [1, 2]. Over the years various studies have been carried out globally to understand the factors that influence the graft function [1]. Multiple factors including technical expertise, donor-recipients related demographics, immunosuppressive regimens, infections, comorbid conditions have been implicated to influence the graft survival [1–3]. Infections are a common cause of morbidity and mortality after transplantation and it is widely known that RT patients have poor resistance to infection [4, 5]. Infections have been ranked second, as a cause of death in RT patients. According to the U.S. Renal Data System, the rate of first infection in the initial 3 years after kidney transplantation is reported to be 45.0 per 100 patient-years of follow-up. It has been postulated that in immunocompromised RT recipients, UTI is the most common infection that affects the graft function and is held responsible for longer hospital stay and increased health care cost [3, 6, 7]. Becerra et al. stated that the length of stay in patients who develop UTI is 74 and 76% higher in men and women renal transplant recipients respectively, when compared to those without UTI [8].

1.2. Burden of the disease

UTI is the most common type of hospital-acquired infection, accounting for nearly 40–50% of all infectious complications among RT patients followed by viral infections, pneumonia and surgical site infections [8, 9]. As per the data from Spanish Network for the Study of Infections in Transplantation (RESITRA) the incidence of cystitis per 100 recipient-years was 13.84 for renal, 3.09 for liver, 2.41 for heart and 1.36 for lung transplant recipients [10]. The incidence of pyelonephritis per 100 recipient-years was 3.66 for renal, 0.8 for liver, 0.3 for heart and 0.6 for lung transplant recipients. UTI-associated bacteremia was seen in 39% of renal, 3% of liver, 3% of heart and none of the lung transplant recipients [11, 12]. The prevalence of UTI in RT patients ranges from 13 to 80% according to various studies [1, 2, 6, 13–16]. Few authors have also reported an incidence as low as 4% to as high as 75% [17–20]. The vast difference could however be attributed largely due to lack of uniform diagnostic criteria to define UTI, implementation of prophylactic regimen and ill-defined period of follow-up. The incidence of UTI in the early post-transplant period (first 6 months) is higher as compared to late periods. However it is this early occurrence of UTI that has a profound effect over the allograft survival. Nearly 84% of symptomatic UTI cases are recorded in the first 6 months after transplant [21].

Recurrent UTI is also one of the major cause that poses threat to renal allograft and the prevalence ranges from 2.9 to 27% in renal transplant recipients. Mohammad et al. reported an incidence of recurrent UTI in nearly 51.7% patients who underwent renal transplantation [22].

1.3. Definition and diagnostic criteria for UTI

A urinary tract infection is an infection causing signs and symptoms of cystitis or pyelonephritis (including the presence of signs of systemic inflammation), which is documented to be caused by an infectious agent. The diagnostic criteria for UTI are similar to those that are used for general population, however all symptomatic UTI are considered as complicated UTI in RT patients [23–25].

Pain and tenderness over the renal allograft or costovertebral region indicates symptomatic infection of the upper urinary tract.

Asymptomatic bacteriuria in women is defined as two consecutive clean-catch voided urine specimens >24 hours apart with isolation of the same organism in quantitative counts of $\geq 10^5$ CFU/mL. However in males a single clean catch urine specimen with isolation of single organism in quantitative counts of $\geq 10^5$ CFU/mL is regarded as asymptomatic bacteriuria. In case of urethral catheterization bacteriuria is defined as isolation of a single organism in quantitative counts of $\geq 10^2$ CFU/mL in a single specimen.

2. Risk factors associated with development of UTI in renal transplant recipients

Post-transplant UTI in renal allograft recipients is of multifactorial origin and is determined by interaction between host factors, abnormalities associated with the anatomy of the urinary tract and the virulence of the pathogenic organisms. A few common extensively studied

factors are listed below. Few studies have found strong correlation of increased predilection to development of UTI, whereas other researchers have not been able to prove the association.

2.1. Gender

Most of the studies show that incidence of UTI is more common in females as compared to male patients who undergo renal transplantation [12]. The mean distance from the urethra to anus is less in females as compared to males, which leads to increased susceptibility for vaginal colonization with uropathogens [14, 26]. Menegueti et al. reported female sex as the only risk factor for post-transplant UTI [27]. Camargo et al. also reported a higher incidence of UTI in female patients [44.4%], despite higher prevalence of male patients in the study. However few studies do report a higher incidence of UTI in males. This could be due to the larger number of male patients receiving transplant in majority of the cohorts [8]. It is well documented that women with recurrent UTI have increased susceptibility to vaginal colonization with uropathogens. Sexual intercourse, using spermicidal products, maternal history of UTI and UTI at an early age predispose these patients to recurrent infections of the urogenital tract [1].

2.2. Catheterization and presence of ureteral stent

It has been observed that increased hospital stay and late removal of the catheter is an independent risk factor for developing UTI [1]. Ostaszewaska et al. reported a strong correlation between occurrence of UTI and length of hospital stay [28]. Stamm et al. reported that the risk of UTI in renal allograft recipients is more by approximately 5% with each day of bladder catheterization [29]. Dantass et al. also had similar observations [30]. Fayek et al. report a higher rate of UTI of 14.2% in transplant recipients with stents as compared to 7.9% without stent [31].

2.3. Anatomical abnormalities

Structural abnormalities of native or transplanted kidney predisposes to increased risk of developing UTI [1, 2]. The anatomical abnormalities could be vesicoureteral reflux, neurogenic bladder or presence of benign prostatic hyperplasia, are usually associated to increased risk for developing UTI [14, 28, 29].

2.4. Immunosuppressants

A wide variety of immunosuppressants are used in transplant medicine either as induction agents or for maintenance therapy. Recipients subjected to antimetabolite (azathioprine or mycophenolate mofetil) and induction therapy with cell depleting antibodies (antithymocyte globulin) are reported to have higher incidence of UTI [1, 32–34]. Prednisone dose of >20 mg/day and multiple rejection therapies are associated with increased risk [35].

2.5. Deceased versus living donor transplants

It has been documented by various studies that the incidence of UTI is more in patients who receive kidney from deceased donor as compared to living donor. Taminato et al., reported that there is a greater risk for the patients who receive organ from deceased donor as against recipients of living donor with an odds ratio of 2.65 [36]. Similar observations were reported

by Ostaszewaska et al., R.Parasuraman et al., Camargo et al., Orhan Deniz Kara et al. and Abdulmalik MA et al. [2, 26, 28, 37, 38].

2.6. Human leucocyte antigen (HLA) match and rejection episodes

HLA compatibility and association with UTI was studied by Ostaszewaska et al. They observed that individuals with more than four HLA mismatches are more likely to develop UTI [28]. Patients who develop rejection episodes show increased incidence of UTI. These individuals are subjected to increased dosages of immunosuppression which may likely predispose these individuals to increased risk of developing UTI [9]. Moradi et al. evaluated the relationship between UTI and biopsy proven chronic rejection in a cohort of 100 patients over a period of 5 years. They concluded that patients with chronic rejection had more episodes of UTI as compared to those without rejection [39].

2.7. Other proposed factors

Apart from the important factors listed above, various other factors have been implicated in developing UTI. Older age has been related to an increased risk for UTI. The same study reported that an increase of 5 years in age at transplant increased the risk for UTI. Benign prostatic hyperplasia and menopause, was an additional risk factor for developing UTI [26, 37, 38]. Delayed graft function (DGF), usually associated with deceased donor organ transplant has been documented as a risk factor for development of UTI [9]. Study reported that occurrence of DGF strongly correlates with the incidence of UTI, with 61.8% patients with UTI developing delayed graft function [28]. Other factors that have been implicated are presence of comorbid conditions like hypertension and diabetes, prolonged cold ischemia time, serum creatinine levels of >2 mg/dL and chronic viral infections [6, 14, 26–28, 35, 37, 39].

3. Etiology of UTI in renal transplant patients

3.1. Etiological agents

The most common type of UTI is bacterial followed by fungi and rarely viruses are implicated in pathogenesis of UTI. Gram negative bacteria are the most common pathogens cultured from the urine of renal transplant patients with UTI, followed by candida and viruses.

3.2. Bacteria

E. coli is the most common, accounting for more than 70% of the cases. Enterobacteriaceae, *Enterococci*, *Pseudomonas* and coagulase-negative *staphylococci* are other common agents. Mycobacterium tuberculosis, Salmonella and Mycoplasma are encountered rarely [2, 6, 38, 41, 42]. A retrospective study by Espinar MJ et al., showed that renal allograft recipients are particularly susceptible to infection by Enterobacteriaceae-producing extended-spectrum β-lactamases (ESBLs). Diabetes mellitus, previous antibiotic prophylaxis or therapy, previous UTI, relapsing infection and patients with delayed graft function after transplant represented risk factors for infection by ESBL positive Enterobacteriaceae. It was also observed that these patients present

early with UTI and exhibit higher resistance to fluoroquinolones, trimethoprim-sulfamethoxazole and gentamicin. Pourmand MR et al. and Tawab et al. studied renal transplant recipients who developed recurrent UTI. *E. coli* was the most common cultured organism from the urine of patients with recurrent UTI. Coagulase negative staphylococci and Bacillus were rare [2, 9, 22].

3.3. Fungus

Candida is the most common cause for UTI in renal transplant recipients and is usually asymptomatic. Serious complications can occur following ascending infections. Fungal balls can be formed that may cause obstruction at the ureterovesical junction [2, 3, 43].

3.4. Viruses

The most common viruses that cause viral UTI in a renal transplant patient are cytomegalovirus and type 1 human polyomavirus (BKV). Clinically they present with fever, acute graft rejection, tubulointerstitial nephropathy and renal vascular disease. BKV-associated nephropathy may be a frequent cause of recurrent post-transplant infections and these patients usually present as sterile pyuria, eosinophiluria and hematuria. Ureteral cell hyperplasia leading to ureteral obstruction has also been reported [2, 3, 40–43].

3.5. *Schistosoma haematobium*

Trematode involves the urinary tract and kidney, and the diagnosis is based on the visualization of parasite ova in urine specimens. The urine should be collected close to noon, when egg excretion is maximal. Reactivation of a prior infection due to immunosuppression has been described in solid organ transplant recipients. Any solid organ transplant recipient from an endemic at risk-area developing hematuria (with or without eosinophilia) should have urine examined to rule out the infection. *S. haematobium* should be treated with praziquantel both in the pre and post-transplant period, as chronic infection can lead to squamous cell carcinoma of the bladder [44].

3.5.1. Causative organisms and identification of the organisms in our cases

Case 1:*The microscopic examination of the urine sediment revealed plenty of pus cells with occasional red blood cells and bacilli. (***Figure 1***). Urine culture study was performed. On nutrient agar large, circular, low convex, grayish, white, moist, smooth and opaque colonies were observed. On MacConkey Agar media the colonies were circular, moist, smooth, and pink and found to be lactose fermenting. (***Figure 1a***) On Gram's stain, pink gram negative rods were identified. (***Figure 1b***) The sample was further subjected to VITEK 2 system for identification and culture sensitivity. Escherichia coli was identified as the causative organism with sensitivity to Piperacillin/ Tazobactum, Sulbactum, Imipenem, Meropenem, Amikacin, Colistin, Levofloxacin and Minocycline. However resistance to Trimetoprim/ Sulfamethoxazole, Gentamycin and Cefepime was observed.*

The patient was treated with intravenous administration of Cefoparazone-salbactam and Levofloxacin for 7 days. Urine routine and culture sensitivity studies were performed on sixth day. There was reduction in the total leucocyte count to 8.4 × 10^6/μl, with normal differential count. The serum creatinine level dropped from 2.4 to 1.8 mg/dL on seventh day. Urine routine microscopic examination revealed

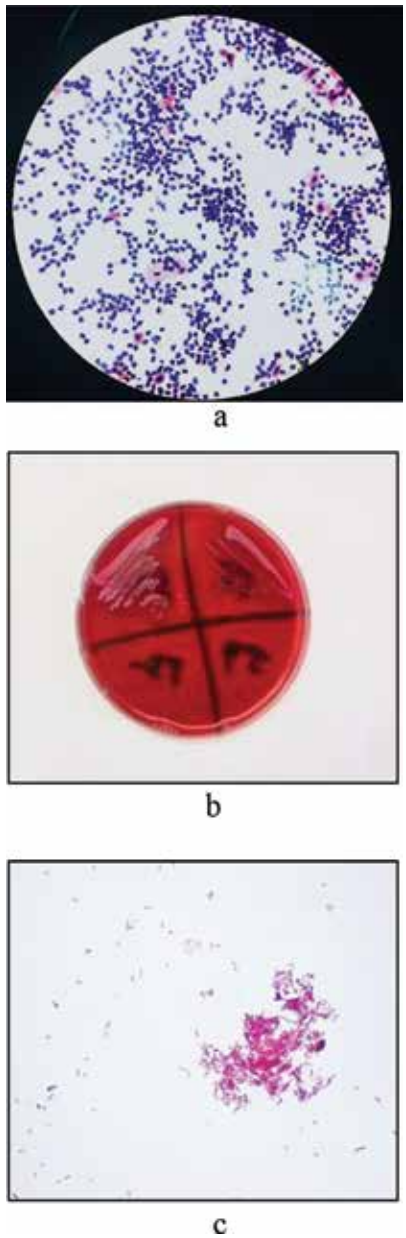

Figure 1. Urine microscopy stained with hematoxylin and eosin stain shows plenty of leucocytes and few bacilli. (Hematoxylin and eosin, x 400). (a) MacConkey agar media with circular, moist, smooth, and lactose fermenting pink colonies. The left upper quadrant is the patient sample and right upper quadrant depicts the positive control. (b) Gram's stain, these bacilli appeared to be as pink gram negative rods (Gram's stain, x 400).

scattered 15–20 WBC/ hpf. The patient was shifted to oral antibiotics for next 3 days. The immunosuppression regimen constituted of Tacrolimus, Prednisone and Mycophenolate sodium. No tapering of the drugs was done. Urine examination and culture studies were negative thereafter. The patient responded well to the treatment and is on regular follow-up. His present serum creatinine is 1.8 mg/dL, 4 months

*after the episode of urinary tract infection.**Case 2:**The microscopic examination of the urine sediment revealed clusters of pus cells, scattered epithelial cells and fungal buds and pseudohyphae. (***Figure 2***) Urine culture study was performed on Sabouraud's dextrose agar. 65 g of the media was suspended in distilled water, mixed to form a uniform suspension, heated, boiled and then sterilized at 118–121°C for 15 min. The urine sample was streaked using inoculating loop and incubated in 37°C for 48 hours. The growth appeared in 48 hours as cream/white colored, smooth and pasty colonies. (***Figure 2a***). A drop of inoculated broth media was placed onto the slide and a drop of lactophenol cotton blue stain was added and examined under the microscope which revealed the presence of chlamydospores. (***Figure 2b***).*

The patient was treated with oral antifungal agent, fluconazole, 100 mg/day for 21 days along with conventional Tacrolimus-based immunosuppressive regimen. Urine routine and culture sensitivity studies were performed on tenth day. There was reduction in the total leucocyte count to 6.35 x 10 ^{6}/μl, with normal differential count. The serum creatinine level dropped to 1.6 mg/dL. Urine examination and culture studies were negative thereafter. The patient responded well to the treatment and is on regular follow-up. Her present serum creatinine is 1.76 mg/dL, 4 months after the episode of urinary tract infection.

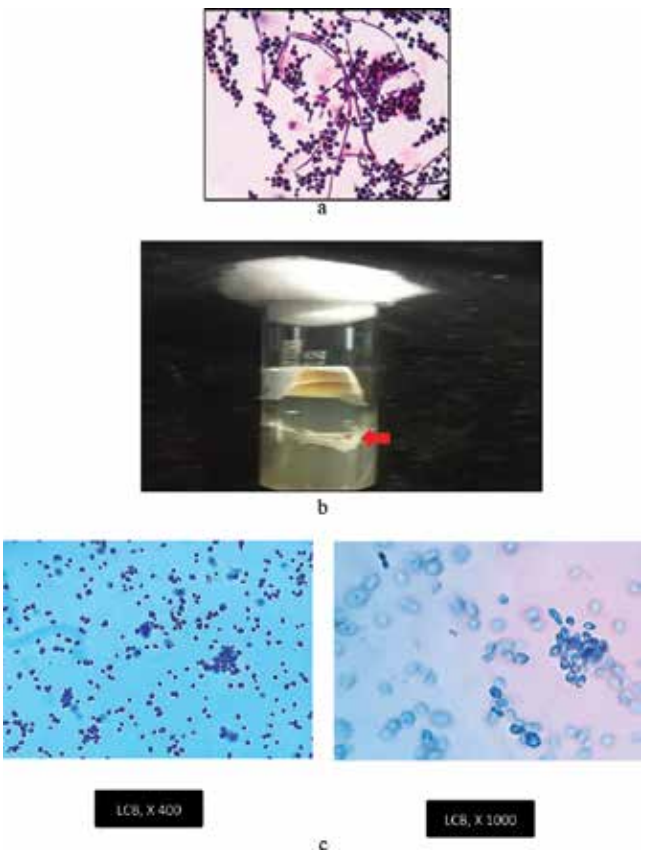

Figure 2. Hematoxylin and eosin stained urine deposit reveals budding fungi along with pseudohyphae. (a) Creamy and smooth colonies of candida on Sabouraud's dextrose agar (red arrow). (b) Lactophenol cotton blue (wet preparation) reveals budding fungi (LCB, X 400)with chlamydospores (LCB, X 1000).

4. UTI and effect on renal allograft function

4.1. Negative impact of urinary tract infections in renal transplant recipients

It has been well documented that development of UTI in renal transplant recipients is associated with increased rates of health resource utilization, which includes length of stay as well as more economic burden. Longer hospital stay exposes these individuals to increased risk of development of nosocomial infection [2, 8].

4.2. Effect on graft function

Mohan et al., in their prospective study of 31 patients who underwent renal transplantation, found that infections in the immediate post-transplant period adversely affected the graft survival. Mortality rate in patients with UTI was reported as 12.9% [9].

Abbott and colleagues undertook a retrospective cohort study of 28,942 Medicare primary renal transplant recipients in the U.S. Renal Data System database from 1996 through 2000, assessing Medicare claims for UTI occurring later than 6 months after transplantation based on ICD-9 codes, and found that the cumulative incidence of UTI during the first 6 months after renal transplantation was 17% (equivalent for both men and women) and at 3 years was 60% for women and 47% for men ($P < 0.001$ in Cox regression analysis). Late UTI was significantly associated with an increased risk of subsequent death and graft loss [45].

In a study by Dhamidharka et al., who analyzed US Renal Data System database over the period of 1996 to 2000 (up to 36 months post-transplant). 265 (30.5%) pediatric patients had either inpatient or outpatient claims for UTI out of total 870 pediatric patients who qualified for the study. The authors found that early UTI (less than 6 months after transplant) was significantly [$P = 0.007$ upon multivariable Cox regression] associated with higher adjusted hazard ratio of graft loss, and late UTI was not associated with such an outcome. Risk for post-transplantation death was not increased significantly after either early UTI (AHR 1.23; 95% CI 0.37 to 4.08) or late UTI (relative risk 2.22; 95% CI 0.90 to 5.44) [46].

Pelle, et al. as well as Giral et al. reported that acute pyelonephritis of the graft is accompanied by renal failure and is an independent risk factor for impaired renal function as well as graft loss [47, 48]. Bodro et al. reported 1-year mortality rate of 3% in patients who developed worsening of graft function secondary to graft acute pyelonephritis. They further discovered that in patients with UTI due to a resistant strain of bacteria, the impairment of graft function is more frequent than in patients who develop UTI due to non-resistant strain bacteria [13]. Several hypotheses have been put forward to explain the negative impact of UTI on graft function. It has been postulated that bacterial infection activated the immune system, which can trigger the rejection cascades leading to acute or chronic rejections, causing deterioration of the graft function. Some authors propose that inflammation secondary to infection can cause scarring of the renal tissue, leading to loss of the functioning nephron mass causing impairment of renal function [49–51]. Reduction in the immunosuppressive agents following an episode of infection may accentuate the rejection process [13].

Various studies like the one by Ostaszewska et al., have found out no significant difference related to UTI and graft survival [28]. Fiorante et al. also in their study of 189 renal allograft recipients, over a follow-up of 36 months, did not find an association between asymptomatic and symptomatic bacteriuria with graft dysfunction. They also did not report statistically significant association between graft dysfunction and acute pyelonephritis of the graft [42]. Similarly, Ariza et al. and Lee et al. did not report any significant graft survival and UTI [52].

5. Management of UTI

Definitive diagnostic and treatment protocols for renal transplant patients are not well-defined. The current treatment protocols depend mainly on the severity of the infection, the local epidemiological data and the results of the culture reports. Complete urinalysis with microscopy along with culture studies is recommended. It has been proposed that bactericidal antibiotics should be preferred to bacteriostatic ones, which might be insufficient to cure the infection since the immune system cannot eradicate the dormant bacteria. Managing the predisposing factors is equally essential. The need for adequate immunosuppression and dose adjustment is also important. Various pharmacological interactions exist between antibiotics used to treat post-transplant UTI and immunosuppressant drugs. Ciprofloxacin and erythromycin are implicated in raising Calcineurin inhibitor (CNI) levels. Levofloxacin and ofloxacin usually do not interfere with CNI levels. Antifungal agents inhibit cytochrome P450 and increase CNI levels. Rifampin, imipenem and cephalosporin can reduce CNI levels. Nephrotoxic antibiotics (e.g., aminoglycosides, amphotericin) may have synergistic effects with CNIs, increasing renal damage.

UTI can co-exist with CMV, BKV and other viral and fungal diseases.

5.1. Management of asymptomatic bacteriuria

No definitive consensus or management is available for treatment of asymptomatic bacteriuria. However many of the researchers agree that there is no need to subject patients with asymptomatic bacteriuria to antibiotics as there are not enough studies that prove that asymptomatic bacteriuria heralds a negative outcome. Also studies have shown that treatment of this entity does not prevent occurrence of significant bacteriuria in the later post-transplant period [39]. Few studies have demonstrated that use of antimicrobials in patients with asymptomatic bacteriuria is usually unsuccessful in removing the offending agent; also it does not prevent the occurrence of subsequent UTI [53]. Study by Goya et al. proposed that considering asymptomatic bacteriuria as a precursor for symptomatic bacteriuria and subsequent development of pyelonephritis and high risk of developing symptomatic UTI in early transplant period that may affect the graft function it is recommended to keep patients with asymptomatic bacteriuria under screening schedules. Treatment with narrow-spectrum antibiotics of short duration of 5–7 days following culture report is recommended [54].

5.2. Symptomatic UTI

Symptomatic bacteriuria is classified further as mild, moderate and severe. Any predisposing conditions have to be treated. For mild cases empirical therapy with oral antibiotics, preferably ciprofloxacin with or without amoxicillin for a period of 5–7 days is recommended. For moderate infections, treatment with ciprofloxacin or ceftriaxone or ampicillin-salbactum is advised for 14 days after the culture sensitivity reports are obtained. For severe symptomatic UTI empirical treatment with pipercillin-tazobactum or cefepime is recommended over a period of 14–21 days following culture sensitivity report. Multi-drug resistant organisms need to be kept in mind before starting the empirical therapy. Carbapenem is the drug of choice for such cases. For recurrent UTI the treatment is extended to 6 weeks.

5.3. Candiduria

In patients with asymptomatic candiduria, there is no recommended treatment. In cases of symptomatic candiduria fluconazole, 200–400 mg, orally per day for 14 days is the treatment of choice. Fluconazole may have drug interactions with Calcineurin inhibitor, hence dose adjustment is recommended. Disseminated cases would require treatment by intravenous amphotericin B, 0.3–1 mg/kg/day for 1–7 days. Flucytosine [25 mg/kg every 6 h for 7–10 days] can also be used, but with caution, especially in cases of renal dysfunction. Monitoring for cytopenias, rash, gastrointestinal symptoms and hepatotoxicity is recommended [55, 56].

6. Prevention

Although the data from various studies does not provide a concrete evidence for post-transplant UTI to have a profound effect on graft dysfunction, but overall it is necessary to control infection related mortality. It is quite obvious from certain studies that UTI or any infection leads to increase in duration of stay at hospital as well as it adds to economic burden as discussed in this review. Infection of any sort can have a psychological effect on the transplant recipient too. With advent of wide range of antimicrobials available as well as vast advancement in the field of transplantation medicine, losing graft function to infections should not be acceptable. Hence it is important to identify the various risk factors and employ strategies to prevent the development of infections in these subset of patients. Individuals with high risk factors like those having structural anomalies of the urinary tract, old age patients, females, presence of comorbid conditions like diabetes, hypertension should be kept under proper surveillance. In case of living donors a thorough screening for infections before transplantation though serological tests, urine analysis and hematology is advisable to rule out possibility of any infections.

Certain studies have emphasized the role of antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) for prevention of UTI. TMP-SMZ is a broad spectrum

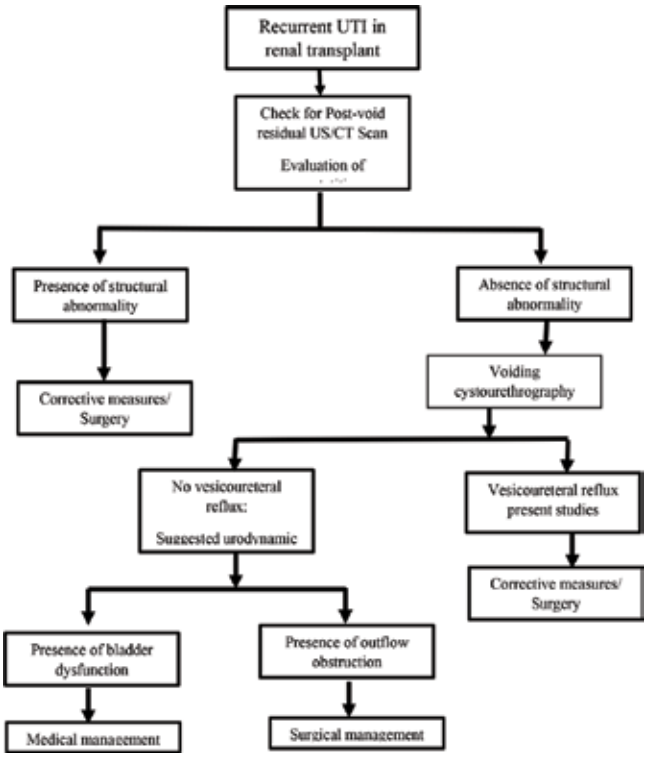

Figure 3. Scheme for evaluating a case of recurrent UTI.

antimicrobial agent, with relatively low cost and is mostly used for prevention of *Pneumocystis carinii* infection [2, 14, 51]. Ariza-Heredia et al. have reported the effect of TMP-SMZ prophylaxis offers great protection to prevent UTI in the first year. Four patients who were not offered this prophylaxis due to certain reasons developed UTI in first year of transplant as against those who received the prophylaxis [14].

In cases with recurrent UTI anatomical and functional abnormalities like vesicoureteral reflux and neurogenic bladder need to be addressed and managed accordingly. The patients should be educated for basic preventive measures like hydration and frequent voiding. Radiological studies should be implicated to rule out the anatomical defects, obstruction, calculi and retained foreign bodies. Prostatitis should be considered as an important differential diagnosis in men who present with recurrent post-transplant UTI. Mitra et al. have proposed a scheme for evaluating a case of recurrent UTI (**Figure 3**) [57].

7. Recommendations

As the risk of UTI is very high in the first week of transplantation, we recommend that every renal transplant recipient should undergo urine routine examination with microscopy for first 10 days in the post-operative period irrespective of the fact that the patient has any

symptoms of UTI. This type of screening will be helpful in early diagnosis and treatment and preventing infection related mortality. Culture studies should be advised as and when required, and the treatment should be planned according to the organisms identified in the culture studies. Antibiotic prophylaxis should be given to patients who are at high risk for developing UTI. Urine examination should be advised during every follow-up. This practice will definitely help in early diagnosis of infection and help in preventing morbidity associated with UTI.

8. Conclusion

Urinary tract infections in the post-transplant period are quite common, more so during the early period of first 3 months. There are various risk factors attributed to development of UTI like female sex, delayed graft function, old age, anatomical anomalies and organs from the deceased donors being more common. Although few studies have identified UTI in post-transplant period as a negative predictor for graft function, further studies are still required to establish this relationship. The criteria to define asymptomatic bacteriuria and UTI are the same as that for general population. However in view of studies that show that post-transplant UTI has deleterious effect on graft function, it is necessary to design standard definitions, protocols for surveillance, prevention and management of UTI in renal transplant recipients.

However our protocol for renal transplant recipients involves regular follow-up by urine routine and microscopic examination and renal function tests, which helps in early detection of infections leading to prompt management. Thus, early intervention in both the patients led to restoration of the renal function with proper graft function.

Conflict of interest

None of the authors report any conflict of interest.

Abbreviations

RT	renal transplant
UTI	urinary tract infection.
CFU	colony forming units.
DGF	delayed graft function.
CNI	calcineurin inhibitors.
TMP-SMZ	trimethoprim-sulfamethoxazole

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Chapter 5

Uropathogenic *Escherichia coli* and Fimbrial Adhesins Virulome

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Additional information is available at the end of the chapter

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Abstract

Urinary tract infections (UTIs) rank second among infectious diseases around the world, and this makes them significant. There are many microbial agents which may cause UTIs. *Enterobacteriaceae* family members are recognized as important UTI bacterial causative agents. Among them, uropathogenic *Escherichia coli* (UPEC) pathotypes are considered as the most important bacterial agents of UTIs. Today, genomics and bioinformatics explain us why UPEC strains are so considerable pathogens regarding UTIs. There is a diversity of *E. coli* strains involving commensal and pathogenic strains. Genomics shows that commensal strains of *E. coli* encompass the minimal amount of genome and genetic elements among *E. coli* populations, whereas the pathotypes of *E. coli* possess the maximal or a big portion of genomic elements. Previous studies confirm the presence of a vast range of virulence genes within the pool of *E. coli* pathotypes like UPEC. So, the pool of virulence genes (virulome) belonging to UPEC enables UPEC pathotypes to have huge genomes with the ability of different levels of pathogenesis. The more virulence factors, the more pathogenicity. Due to the presence of a mass of virulence factors within UPEC cellular structures, well-known fimbrial adhesins in UPEC pathotypes are discussed in this chapter.

Keywords: uropathogenic *Escherichia coli*, genomics, fimbriae, adhesins, virulence factors, urinary tract infections

1. Introduction

Every year, several million people suffer from urinary tract infections (UTIs), and of course it costs expensive for governments and healthcare medicine centres [1, 2].

UTIs with second ranking are one of the most dominant infectious diseases around the world. Although UTIs include vast etiological microbial agents, two pathogenic microorganisms

such as *Escherichia coli* (*E. coli*) (as a predominant pioneer bacterial agent) and Candida albicans (C. albicans) (as a predominant pioneer fungal agent) are the most recognized UTI etiologic pathogens [3–6].

The pangenomic and phylogenetic studies have revealed five different categories within the species of *E. coli*. These five categories involve A, B1, B2, D and E, which depending on their strains can cause extra- and intra-intestinal infections. The extra-intestinal pathogenic *E. coli* (ExPEC) may lead to a vast range of infectious diseases. So, uropathogenic *E. coli* (UPEC) represents one of the most important causative bacterial pathotypes of UTIs. Three phylogroups of A, B1 and E encompass intra-intestinal commensal and/or pathotypes of *E. coli*, whereas the B2 and D phylogroups involve, respectively, the most and the least numbers of UPEC pathotypes [7, 8].

1.1. Biology of urinary tract infections

There are different types of UTIs with a diversity of clinical demonstrations. Today, we know that the UTI syndromes are completely in association with hosts' immune system activities, type of causative microbial agent and the contributed microbial virulence factors. UTIs may be appeared as acute or chronic lower (typically known as cystitis) and/or upper (typically known as pyelonephritis) urinary tract infections, with symptomatic or asymptomatic manifestations and complicated or uncomplicated demonstrations. So, asymptomatic bacteriuria and simple cystitis with some ignorable irritations may be recognized as light and mild UTIs, respectively; while the urosepsis is known as a serious deathful type of UTI. Generally, the uncomplicated UTIs are recognized in patients with no previous background for UTIs, whereas the complicated UTIs normally happen in patients with previous problems in their urinary tracts. The remarkable point of view is the association between predisposing factors of diabetes, sexual intercourse, gender, catheterization, pregnancy, overweight, genetic factors, host's immune system responses and the type of UTIs and their severities [3, 5, 8–12].

In accordance with previous surveys, there are several numbers of microbial pathogens which can be identified as UTI pathogenic microorganisms. The microbial pathogens depending on the type of UTIs involve a vast number of pathogenic causative agents including Gram-negative bacteria, e.g. UPEC, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Citrobacter* spp., *Morganella morganii*, *Acinetobacter* spp., *Salmonella* spp. and *Pseudomonas aeruginosa*; Gram-positive bacteria such as Staphylococcus aureus *(methicillin-sensitive* S. aureus (*MSSA*) and/or *methicillin-resistant* S. aureus (*MRSA*)), Staphylococcus epidermidis (*methicillin-sensitive* S. epidermidis (*MSSE*) *and/or methicillin-resistant* S. epidermidis (*MRSE*)), *Staphylococcus saprophyticus*, *Streptococcus* spp., *Enterococcus faecium*, *Enterococcus faecalis*, diphtheroids and *Corynebacterium urealyticum* and fungal agents like C. albicans, Candida glabrata and Candida tropicalis. As aforementioned, some pathogens are predominant in complicated UTIs, and some others are responsible for uncomplicated UTIs; however, the UPEC strains are common causative agents in both types of complicated and uncomplicated UTIs. Moreover, the presence of living microbial cells determines the condition of UTIs. The usual threshold for UTI pathogens is estimated $\geq 10^5$ living cells per urine millilitre (ml). As each living cell can grow

and create its own colony, the 10^5 cells can be construed as 10^5 colony-forming units (CFUs). But we have to notice that, in some cases, the aforementioned threshold must be counted less than 10^5 CFUs/ml [3, 6, 10–14].

1.2. The genus of *Escherichia*: A great bacterial empire

The genus of *Escherichia* includes *E. albertii*, *E. coli*, *E. fergusonii*, *E. hermannii*, *E. marmotae* and *E. vulneris*. The familiarity of these species is shown in **Figure 1**. In addition to these species, there are some *Escherichia* strains which have no differences in their phenotypes; but from the genotypic aspects, they have different characteristics. These strains are named as cryptic clades, which are branched into five strains of C-I to C-V [15–18].

E. coli is the most famous member of Gram-negative bacterial family of *Enterobacteriaceae* which was identified by Theodor *Escherich*. This non-spore forming and generally motile (with a peritrichous flagellated arrangement) facultative anaerobic rod-shaped bacterium was named *E. coli* by the suggestion of Castellani and Chalmers in 1919 [7, 19, 20]. There are a diversity of *E. coli* strains which are divided into commensal types (intra-intestinal non-pathogenic strains) and pathotypes (intra-intestinal pathogenic *E. coli* (InPEC) and extra-intestinal pathogenic *E. coli* (ExPEC)). The commensal types of *E. coli* are able to be settled within the infants' alimentary canal just in some hours after birth as beneficial normal flora populations [21, 22].

The *E. coli* pathotypes are divided into a vast range of strains which may cause different types of infectious diseases. **Table 1** indicates the pathotypes and their related infections. In accordance with the table, the pathotypes have been divided into three groups: ExPEC, InPEC and ShiToPInPEC. Phylogenetic studies show a close relationship between *Shigella* spp. and *E. coli*. A close genetic similarity is recognized between *Shigella* spp. and enteroinvasive *E. coli* (EIEC) pathotypes [4, 7, 23–30].

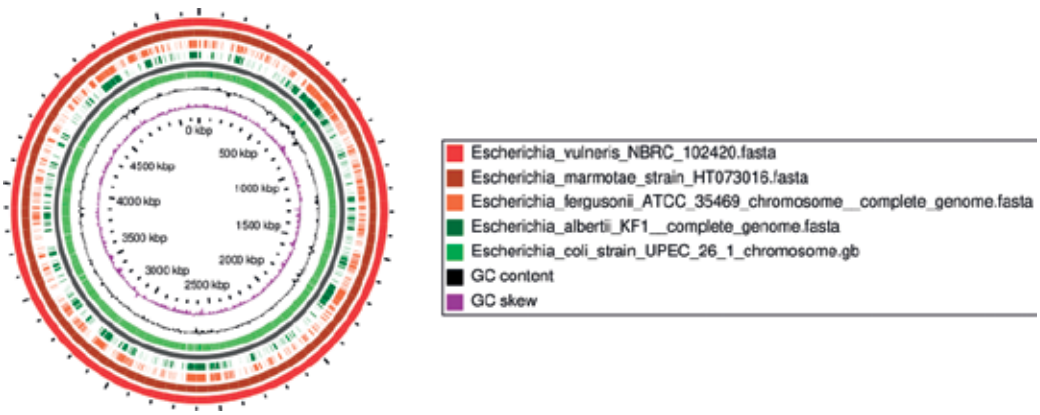

Figure 1. The genome of uropathogenic *E. coli* (UPEC) has been compared with *E. albertii*, *E. fergusonii*, *E. marmotae* and *E. vulneris* by the online GView Server system. The figure indicates genomic familiarities between the *Escherichia* species. As shown, the species of *E. marmotae* and *E. vulneris* have very close genomic similarities with UPEC, whereas there is some dissimilarity between genomic treasures of *E. albertii*, *E. fergusonii* and UPEC (GView Server; https://server.gview.ca/).

Category	Pathotype	Type of infection	Appearance	Phylogroup
ExPEC	Neonatal Meningitis E.coli (NEMEC)	Meningitis in neonates	Opportunistic	D, E
	Septic E.coli (SEPEC)	Sepsis	Opportunistic	B1
	Uropathogenic E.coli (UPEC)	Urogenital tract infections	Opportunistic	B2, D
InPEC	Entero -Aggregative E.coli (EAEC)	Diarrhoea (bloody)	Pathogenic	A, B1, D, E
	Entero -Pathogenic E.coli (EPEC)	Diarrhoea (bloody)	Pathogenic	
	Entero -Toxigenic E.coli (ETEC)	Diarrhoea (bloody)	Pathogenic	
Shigella Toxin Producer InPEC (ShiToPInPEC)	Entero -Hemorrhagic E.coli (EHEC)	Bloody Diarrhoea	Pathogenic	B1, D, E
	Entero -Invasive E.coli (EIEC)	Bloody Diarrhoea	Pathogenic	A, B1, E
	Adhesive -Invasive E. coli (AIEC)	Bloody Diarrhoea	Pathogenic	B2
	Diffused -Adhesive E.coli (DAEC)	Bloody Diarrhoea	Pathogenic	A, B2, D

Table 1. The categorization of *E. coli* pathotypes, the related infections and the condition of appearance.

2. *Escherichia coli* and pangenomics

E. coli is a quite diverse genus which involves a vast range of strains with different metabolic properties, pathogenesis, genomic treasure, virulence factors and ecological varieties. These characteristics make *E. coli* an important case in association with infectious diseases. The *E. coli* strains range from commensal strains (useful normal flora) to AIEC, DAEC, EAEC, EHEC, EIEC, EPEC, ETEC, NEMEC, SEPEC and UPEC pathotypes. The characteristic diversities among *E. coli* strains are completely pertaining to their specific pangenomes. The type of genes and the gene pool of microorganisms determine the quality and the quantity of genetic evolutionary properties [4, 7, 22].

The term pangenome was applied by Sigaux for a database with the content of tissues and tumour genomic data; but the application of pangenome with its microbial content was used by Tettelin and colleagues for the first time, and this refers to a collection of genes and genetic elements in a family group which can be recognized among species of a genus. According to genomic studies, each microbial genus encompasses a main genomic pool which is known as core genome. The core genome contains all those vital genes belonging to different species of a microbial genus. In addition to core genome, there is a group of genomic materials pertaining to species members of a genus which is named as extra genome (flexible or accessory genome). Sometimes some accessory genome pools contain unique genes which are completely related to specific strain. The extra genome possesses genes that are vital but varies in different genome pools. Some genera bear closed pangenomes, whereas the others contain open pangenomes. The open pangenomic microbial organisms involve a vast range of strains. In parallel with molecular techniques, bioinformatics has a key role in pangenomics. Computational analyses give us brilliant information regarding chromosomal genes and motile genetic elements such as plasmids, transposons and phages. Today, the bacterial genus of *E. coli* is known as the most progressive prokaryote with the highest detected genomic sets [7, 31–34].

The complete genomic data regarding *E. coli* (K12 strain) was reported in 1997 for the first time. Due to the recent aforementioned information regarding *E. coli* genomics, we now know that

each strain comprises core genome, accessory genome (extra genome and/or flexible genome) and some unique genes which are specific for each strain. Furthermore, the accessory genomic pool which is flexible may contain integrons, pathogenicity islands (PAIs), phages, plasmids, prophages and transposons. The presence of these genomic elements is related to the nature of the environment in which bacterial cells exist. So, the size of genome is completely dependent on the habitat of bacteria. In another word, the condition of genomic pool and sequence of the genome determine the biological characteristics of the bacteria. Therefore, genomics of *E. coli* strains reveal the needs of them in their own habitats [7, 23, 35].

The reported results from previous studies show that the commensal strains of *E. coli* bear the smallest pangenome (with no virulence genes or with minimal capacity), whereas the pathogenic strains of *E. coli* like UPEC pathotypes encompass large pangenomes (because of the presence of a mass of virulence genes). So, the added genes in pathotype pangenomes are recognized as virulence genes (virulome). It is estimated that UPEC pathotypes carry 10^5 bp much more than commensal strains within their pangenomes. This property gives a high plasticity to UPEC pathotype pangenomes. As shown in published reports, the pangenome of *E. coli* strains involve 4.6–5.9 Mbp and the chromosomal genomes are consisted of limited number of genes [7, 23, 26, 36].

Table 2 shows a number of well-known databases in which the genomic data regarding *E. coli* genomes are accessible.

Database	The main subject	URL	Reference
EcoCyc *E. coli* Database	*Escherichia coli* K-12 MG1655	https://ecocyc.org/	[37, 38]
EcoGene 3.0	*Escherichia coli* K-12	http://ecogene.org/	[39]
Kyoto Encyclopedia of Genes and Genomes (KEGG)	Genes, genomes, etc.	http://www.genome.jp/kegg/ http://www.genome.jp/kegg/	[40]
SHared Information of GENetic Resources (SHIGEN)	The profiling of *Escherichia coli* chromosome (PEC) database	https://shigen.nig.ac.jp/ecoli/pec/	[41]
Pfam 31.0	Protein family database	http://pfam.xfam.org/	[42]
Ensembl Genomes (The European Bioinformatics Institute (EMBL-EBI))	Genomes	http://ensemblgenomes.org/	[43]
The DNA Data Bank of Japan (DDBJ)	Nucleotide sequence database	http://www.ddbj.nig.ac.jp/	[44]
GenBank (National Center for Biotechnology Information (NCBI))	Nucleotide sequence database	http://www.ncbi.nlm.nih.gov/genbank/	[45]

Table 2. Some useful and helpful databases which can be used for *Escherichia coli* pangenome.

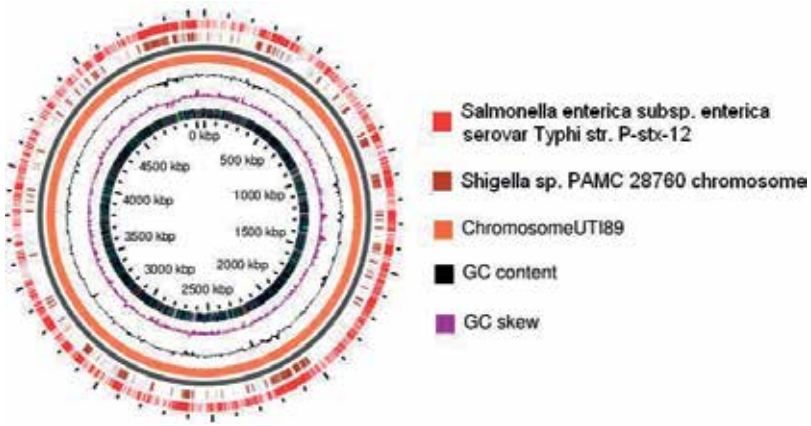

Figure 2. A chromosomal comparison between UPEC (UTI89), *Shigella* sp. and *Salmonella enterica*. The GC content and GC skew are shown, too (GView Server; https://server.gview.ca/).

The pangenomic studies reveal an interesting evolutionary relationship between *E. coli*, *Shigella* spp. and *Salmonella enterica*. It seems that *E. coli* is the ancestor of *Shigella* spp. The *Shigella* spp. have derivated from *E. coli* pathotypes within a duration of 270,000–35,000 years, whereas the origination of *E. coli* and *S. enterica* bacteria from a common progenitor goes back to 100,000,000 years ago [4, 46] (**Figure 2**).

3. Uropathogenic *Escherichia coli* (UPEC)

The UTIs are divided into community-acquired and nosocomial infectious diseases. The UPEC pathotypes are the most dominant causative bacterial agents of UTIs. As previous investigations show, about 50% of nosocomial and up to 95% of community-acquired UTIs are occurred by UPEC strains. So, the UPEC pathotypes are one of the most considered UTI causative agents worldwide. These reports lead us to a wide variety of virulence factors in UPEC pathotypes. Besides, the bioinformatic approaches and pangenomics confirm the presence of a giant treasure of virulence genes within the pangenome of UPEC [7, 8, 35, 47].

The spread of virulence genes among UPEC pathotypes is quite different. The range of UTIs varies from ignorable cases like asymptomatic bacteriuria to deathful cases like urosepsis. The severity of UTIs is completely in association with the UPEC virulence gene pool (virulome). Sometimes, pathotypes undergo mutations in their hosts' bodies which may lead to lose their own virulence genes. It seems that the UPEC pathotypes, which may cause asymptomatic bacteriuria, have undergone virulence gene deletions. On the other hand, strong uropathogenic strains encompass a mass of virulence genes which enable them to occur severe UTIs within their hosts' bodies. The occurrence of UTIs is associated with the host's genetic predisposing factors, immune system, gender, hospitalization, catheterization, social behaviour, sexual activities, personal hygiene and the presence of virulence factors in uropathogenic microbial agents [3, 7, 11, 13, 22, 48–50].

The outcomes of several studies reveal the presence of a huge number of virulence factors which have been expanded among different strains of UPEC. Here, the most considerable virulence factors are mentioned and the most considerable filamentous adhesins are explained one by one.

4. Uropathogenic *Escherichia coli* (UPEC) virulome

The severity of UPEC pathogenesis is completely in association with diversity of virulence genes in their pangenomes. **Figure 3** shows the pangenome of UTI89. The virulence genes may be located on chromosomes (added through vertical gene transfer) or plasmids, transposons, integrons and phages (added via horizontal gene transfers). Previous studies indicate that the majority of virulence genes belonging to UPEC are located on pathogenicity islands (PAIs) where many of genes are transferred from other species rather than *E. coli* through the feature of horizontal genomic exchange. UPEC pathotypes are effective pathogens due to their high capacity of virulome. The diversity of virulence factors enables UPEC to manifest different types of UTIs in their human hosts. Adhesion, immune system escape mechanisms, iron uptake systems, protease enzymes and toxins are the most significant mechanisms that UPEC pathotypes should utilize them to survive in the human host urinary tract [22, 51–53].

Because of the vast variety of pathogenicity potentials in UPEC strains, only hair-like structures of afimbrial adhesins (including curli and Afa) and fimbrial adhesins (comprising Dr, Type 1 fimbriae, Type 3 fimbriae, F1C fimbriae, S fimbriae, P fimbriae, Auf and F9 fimbriae) are discussed in this chapter. There are some useful databases such as Center for Genomic Epidemiology (https://cge.cbs.dtu.dk/services/VirulenceFinder/) and Virulence Factors of Pathogenic Bacteria (http://www.mgc.ac.cn/VFs/) which may be used for detection and identification virulence genes within the *E. coli* strain populations' genomes [54].

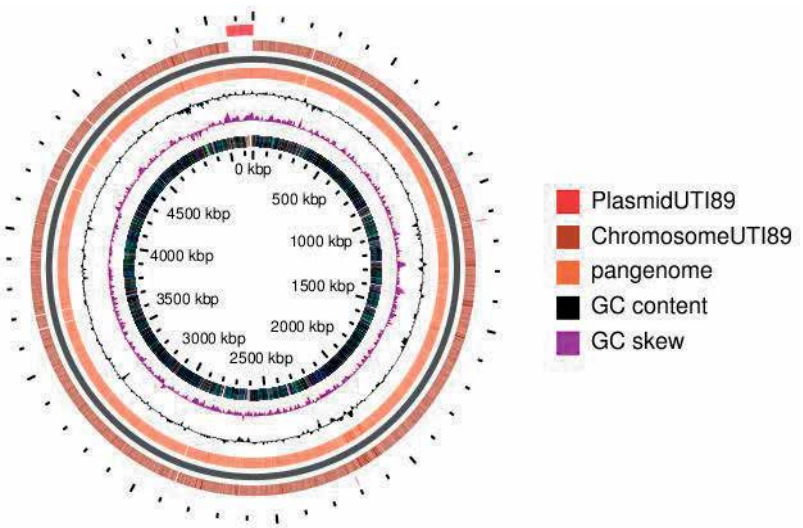

Figure 3. The pangenome map (chromosomal and plasmid genomes) of UPEC (UTI89). The GC content and GC skew are shown, too (GView Server; https://server.gview.ca/).

4.1. Filamentous adhesin virulome

Each microorganism either pathogen or non-pathogen needs to be adhered for colonization. Indeed, colonization of pathogenic microorganisms results in pathogenesis within human body's host. For this reason, UPEC has a range of superficial proteins and adhesins (**Table 3**). However the hair-like structured fimbriae are invaluable virulence factors which enable UPEC pathotypes to have successful attachment, colonization, biofilm formation and virulence [7, 22, 53, 55–65].

Fimbrial adhesins are superficial peritrichous arranged exterior proteinaceous appendages which target special motifs upon the cell surface receptors to join them in the manner of key-and-lock operation. These adhesins are able to attach onto biotic (e.g. host cells) and abiotic (e.g. catheter) surfaces. The aforementioned characteristics make UPEC bacteria functional and effective pathogenic microorganisms. The attachment of bacterial cells of UPEC onto the host cells is a complicated process which may be caused by important proteinaceous molecules of adhesins. Adhesins prepare suitable condition for a successful signalling controlled communication between UPEC cells and human body cells. In other words, the fimbrial adhesins act as signal molecules. As shown in **Table 3**, the most studied and recognized superficial filamentous adhesins are Curli, Dr, AFA, Type 1 fimbriae, Type 3 fimbriae, F1C fimbriae, S fimbriae, P fimbriae, F9 fimbriae and Auf. Some of these superficial fimbrial organelles involving F1C, P, S, Auf, Type 1, Type 3 and F9 fimbriae are categorized into chaperone-usher (CU) proteins [8, 27, 53, 59, 62, 66].

4.1.1. Curli adhesins

Curli adhesins of UPEC are known as types of fragile exterior proteinous coiled fibrous appendages which contribute in linking the UPEC cells onto related receptors situated upon the human body cells such as endothelial cells, epithelial cells, matrix proteins, urothelial cells, mucosal cells, blood cells, etc. In addition to UPEC pathotypes, curli adhesins are recognized in *Salmonella* spp. too. The affinity between curli organelles and Congo red makes it easy to observe these tiny adhesins by microscope. Curli adhesins with up to 12 nm width and 1 μm length are made of CsgA (curlin as major content with amyloid property) and CsgB (as minor content with amyloid property and nucleator activity) proteins. The highly conserved curli gene clusters in UPEC pathotypes are organized into *csgBAC* and *csgDEFG* operons. Curli molecules are effective structures to adhere UPEC cells onto the urine bladder and kidney urothelial cells within human bodies [50, 52, 53, 57, 67–69] (**Table 3**).

4.1.2. Dr/Afa adhesins

The Dr and Afa adhesins are the members of DR family. Dr adhesins (with a homology rate of ≥70%) and Afa molecules are able to bind to the Dr^a blood group antigen molecules situated onto the decay-accelerating factors (DAFs). The DAF molecules are located upon the surface of different types of cells such as urothelial cells. The Dr gene operons consisted of five genes, including *draA–draE*, which are detectable in 7% of the UPEC populations. The *draE* gene is responsible for Dr haemagglutinin production, which is contributed in type IV collagen attachment. *draA–draG* genes are highly conserved and produce the accessory

proteins, whereas the *draE* genes with lower conserved sequences are responsible for adhesin structural subunits. Moreover, the AFA adhesins are encoded by a five-member gene operon including *afaA*, *afaE*, *afaD*, *afaB* and *afaC*. The proteins of AFAI and AFAIII are known as Dr family members. In accordance with previous studies, some of Dr and AFA adhesins have close similarities with chaperone-usher pathway adhesins. The AFA adhesins are recognized in up to 65% of UPEC pathotypes causing cystitis, 26% causing pyelonephritis and 6% asymptomatic bacteriuria (ABU) [7, 8, 22, 55, 61, 70, 71] (**Table 3**).

4.2. Chaperone-usher fimbrial adhesins

There are varieties of fimbriae which are produced by Gram-negative bacteria such as *Enterobacteriaceae* family members. The subunits of these fimbriae are assembled by different pathways like CU pathway. Those fimbriae produced via CU pathway are the most frequent filamentous organelles among Gram-negative bacteria populations. The CU pathway is a kind of common bacterial secretion system with a high conservancy. In a fimbrial CU pathway, chaperone (a periplasmic protein molecule) together with a pore-forming protein of usher (situated within bacterial outer membrane) orchestrate this secretion system. So through the CU pathway, the usher protein plays its role as platform assembler by employing a chaperone to produce and secrete subunits of CU fimbriae class. F1C, P, S, Auf, Type 1, Type 3 and F9 fimbriae in UPEC pathotypes are known as CU pathway proteinaceous adhesins [62, 66, 72–75] (**Table 3**).

4.2.1. Type 1 fimbriae

Type 1 fimbriae as mannose-sensitive adhesins (belonging to chaperone-usher class) are able to attach to those receptors with mannose residues. Uroplakin molecules with high frequency in human urine bladder are known as one of the most important Type 1 fimbriae receptors. Furthermore, there are different types of Type 1 fimbriae receptors which are located on human ureter and Henle's tubules. These fimbriae are encoded in 99% of commensal and pathogenic strains of *E. coli* including UPEC pathotypes. As important virulence factors, Type 1 fimbriae have peripheral arrangement upon the microorganisms' surfaces with a number of 1–5 hundred. Type 1 fimbriae with up to 10 nm width and up to 2 μm length are able to perform haemagglutination. The Type 1 fimbriae are encoded by the highly conserved gene operon consisted of nine genes of *fimBEAICDFGH*. The FimH protein which is located on the top of Type 1 fimbria is recognized as the main adhesin. FimG, Fim F and FimA protein molecules are, respectively, situated under the FimH molecule. FimC and FimD play their roles as chaperone and usher proteins, respectively. The recombinase enzymes of FimB and FimE activate as bidirectional switching molecules for turning on and/or turning off the cluster gene expression. The activities of FimB and FimE are directly associated with environmental factors [7, 22, 50, 53, 55, 60, 62, 68, 71, 74, 76, 77] (**Table 3**).

4.2.2. Type 3 fimbriae

Type 3 fimbriae are encoded by *mrk* gene operon of *mrkABCDEF* in UPEC and other members of *Enterobacteriaceae* family such as Klebsiella pneumoniae. The highly conserved gene

of *mrkB* encodes chaperone protein of MrkB, whereas the MrkC plays role as usher protein. MrkA and MrkF are the major and minor subunits in Type 3 fimbriae, respectively. The adhesin molecule of Type 3 fimbria is recognized as MrkD and MrkE plays its role as a regulator protein. It seems that *mrk* gene cluster originally belongs to K. pneumoniae which has been horizontally transferred into UPEC pathotypes by plasmids. The role of Type 3 fimbriae in biofilm formation regarding catheter-associated urinary tract infections (CAUTs) is significantly considered [53, 56] (**Table 3**).

4.2.3. F1C fimbriae

The F1C fimbriae are encoded by a gene operon consisting of seven genes of *focAICDFGH*. F1C fimbriae are expressed by up to 30% of UPEC pathotypes. The F1C fimbria is composed of FocA (major fimbrin subunits), FocF and FocG (minor fimbrin subunits) proteins. On the top of F1C fimbria, FocH monomer is located which acts as an adhesin. So, F1C fimbriae adhere onto the receptors with galactosylceramide (situated on the surfaces of urothelial cells of the urinary bladder, kidneys and ureters) and globotriaosylceramide (located in kidneys) residues. Previous surveys indicate a strong attraction between F1C fimbriae and Gal-NAc-beta-1-4-Gal-beta structure of glycolipids. FocC and FocD proteins are recognized as chaperone and usher molecules, respectively. Due to prior scientific investigations, the F1C fimbriae are able to bind to their specific receptors upon the whole zone of the urinary tract. There is a close homology between F1C and S fimbriae [7, 53, 55, 62, 66, 78] (**Table 3**).

4.2.4. S fimbriae

In addition to FIC, the S fimbriae organelles have also a close morphology to F9, P and Type 1 fimbriae and are detected in ≥22% of the UPEC pathotypes. The S fimbriae are encoded by *sfa* gene operon with nine genes. SfaA, SfaS and SfaH proteins contribute in S fimbrial adhesion. The SfaA protein is a dominant subunit, and the minor subunits are composed of SfaG, SfaH and SfaS. SfaS is located on the top of S fimbriae and adhere to alpha-sialyl-2,3-alpha-galactose residues upon the glycoproteins of urothelial tissues of the urinary bladder and kidneys. The presence or absence of S fimbriae is determined by environmental factors. The related regulations and phase variations are done by SfaB and SfaC [7, 22, 35, 50, 53, 55, 62, 66, 71, 77, 79] (**Table 3**).

4.2.5. P fimbriae

P fimbriae as considerable adhesins are encoded by 11 genes within a gene operon of *papA-K* in up to 70% of UPEC pathotypes. The predominant subunit in P fimbria is PapA fimbrin placed in the basis of the fimbrial stalk. PapG is known as the main adhesin which is linked to the stalk by PapE, PapF and PapK proteins. PapD and PapC have chaperone and usher roles, respectively. There are some isoclasses for PapG (PapGI, PapGII (major isoclass in UPEC strains) and PapGIII) in different UPEC pathotypes. The related receptor epitopes of P fimbriae are alpha-D-galactopyranosyl-(1-4)-beta-D-galactopyranoside which are located on the surface of entire urothelial cells covering the human urinary tract. P fimbriae are recognized as significant virulence factors in UPEC virulome [7, 22, 50, 53, 62, 66, 71, 77] (**Table 3**).

4.2.6. Auf fimbriae

Auf (acronym for another UPEC fimbria) fimbriae are detected in 67% of isolated UPEC pathotypes. The Auf fimbriae are encoded by the gene operon of *aufABCDEFG*. AufA protein is predominant subunit in Auf fimbria, whereas AufC is known as an usher protein. The Auf protein receptors are still unknown in human body cells [7, 22, 53, 62, 74] (**Table 3**).

4.2.7. F9 fimbriae

The F9 fimbriae encoded by *f9* gene operon including *c1931–c1936* are detectable in 78% of UPEC populations. The C1931 protein is the major subunit identified in F9 fimbriae. The genetic and structural characteristics of F9 fimbriae are very close to Type 1, F1C and S fimbriae. Gal-beta-(1-3)-Glc-NAc and lacto-N-tetraose glycans are recognized as the main F9 fimbriae receptors [22, 53, 59, 60] (**Table 3**).

5. Diagnostic methods for virulence genes of filamentous adhesins

Detection and identification of genes such as virulence genes of filamentous adhesins may be achieved by a vast range of molecular techniques. PCR tools from conventional and multiplex to real time are the commonest molecular diagnostic techniques which can be used for limited samples [80–86].

Furthermore there are advanced pangenomic techniques like microarray technology which can be applied for detection and identification of different types of genes, when there are huge numbers of specimens. Microarray technology is divided into three types of DNA, protein and RNA microarray tools. The outcome of microarray technology is reliable, sensitive, specific, flexible and rapid with high accuracy [4, 7, 8, 87–93].

6. Conclusion

UPEC strains are expanded pathogenic microorganisms which are able to carry a mass of virulence genes within their genomes. The environmental condition and the genomic abilities and capacity determine the expression of virulence genes and factors. The UPEC strains bear different types of virulence factors in different parts of their cellular structures. These properties make UPEC pathotypes interesting pathogenic microorganisms which can appear a vast range of UTIs: from acute to chronic, from light to severe, from complicated to uncomplicated, from lower to upper and from asymptomatic to symptomatic signs and syndromes. So, knowing the genotypic and phenotypic characteristics of UPEC strains in different regions of world helps us to recognize the probable UPEC strains with their local clinical demonstrations. This enables us to have an accurate diagnosis with a definite treatment to reduce the healthcare costs around the world. Moreover, equipped microbiology laboratories with normal molecular tools and techniques like PCR or advanced pangenomic technologies support us to have specific, sensitive and reliable outcome.

Adhesins	Type of adhesins	Genes	Role	Target structure	Type of UTIs
Curli	Afimbrial adhesin	*csgA, csgB,csgC, csgD, csgE,csgF,csgG*	Adhesion for colonization (biofilm formation) and invasion	Matrix Proteins like Fibronectin, Laminin and Plasminogen, Mucosal cells	Severe UTIs; Cystitis in particular
Dr	Fimbrial adhesin	*dra* gene family including: *draA, draB, draC, draD, draE, draP*	Adhesion for colonization, Preparing invasion	A vast range of cells with Dr blood group antigen on their surfaces like urothelia, Neutrophil cells, Connective tissues in upper part of human urinary tract	(Recurrent and/or chronic) Cystitis and pyelonephritis (mostly in pregnant women), Asymptomatic Bacteriuria (ABU) in few cases
AFA	Afimbrial adhesin	*afa* gene family including: *afaI, afaII, afaIII ,afaIV,nfa1 ,drII*			
Type 1 fimbriae	Fimbrial adhesin (sensitive to mannose)	*fim* gene family including: *fimA, fimB, fimC, fimD, fimE, fimF, fimG, fimH, fimI*	Adhesion for colonization (biofilm formation), invasion	Red Blood Cells (RBCs), Mucosal membrane and Epithelium cells, Uroplakin receptors in urine bladder	UTIs
Type 3 fimbriae	Fimbrial adhesin	*mrk gene familyincluding: mrkA, mrkB, mrkC, mrkD, mrkE, mrkF*			UTIs in catheterized patients
F1C fimbriae	Fimbrial adhesin	*focA, focC, focD, focf, focG, focH, focI*	Adhesion for colonization (biofilm formation)	Glycolipids of endothelia, Mucosal membrane and Glomeruli	UTIs, Pyelonephritis in particular
S fimbriae	Fimbrial adhesin	*sfuA, sfaB, sfaC, sfaD, sfaE, sfaF, sfaG, sfaH, sfuS, sfaX, sfaY*	Adhesion and colonization	Sialic acid molecules on kidneys and glomeruli endothelial, epithelial and mucosal cells	Upper UTIs in most cases
P fimbriae	Fimbrial adhesin Resistance to mannose	*papa, papB, papC, papD, papE, papF, papG, papH, papI, papJ, papK*	Adhesion and colonization	vascular epithelia, urothelia and Mucosal cells	Acute forms of UTIs (particularly Pyelonephritis), ABU in few cases
F9 fimbriae	Fimbrial adhesin	*c1931, c1932, c1933, c1934, c1935, c1936*	Adhesion for colonization (biofilm formation) ?	Urothelial cells ?	UTIs ?
Auf fimbriae (Another UPEC Fimbriae)	Fimbrial adhesin	*aufA, aufB, aufC, aufD, aufE, aufF, aufG*	Adhesion for colonization (biofilm formation)	unknown	UTIs

Table 3. The UPEC fimbrial and afimbrial adhesins and their characteristics within human bodies [7, 22, 53, 55–64, 71].

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Chapter 6

Resistant Gram-Negative Urinary Tract Bacterial Infections

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Additional information is available at the end of the chapter

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Abstract

Urinary tract infection (UTI) is one of the most common infections in both the community as well in hospital settings. It is mostly caused by Gram-negative bacteria (GNBs). Over the past two decades, GNBs have developed complex mechanisms of resistance against most of the potent antibiotics. This has been a global challenge which has been identified by the World Health Organization as "one of the greatest threats to human health." This crisis is mostly attributed to the overuse and misuse of these medications, as well as lack of new drug antimicrobials by the pharmaceutical industry. This resulted in prolonged hospital stay, marked increase in the cost as well as increase in morbidity and mortality. Furthermore, it increases the risks and complications of urological procedures. In this chapter, we review the management of the most common and challenging group of resistant Gram-negative organisms, the extended-spectrum β-lactamases producing organisms (ESBL) and the carbapenem-resistant organisms (CRE/CRP). The latter group includes carbapenem-resistant *Enterobacteriaceae* (CRE), as well as *Pseudomonas aeruginosa* carbapenemases (CRP). When treating these infections, clinicians have few effective antimicrobials options. A critical step in managing these organisms is the early recognition and appropriate empiric therapy. Both showed morbidity and mortality benefits.

Keywords: urinary tract infection (UTI), Gram-negative bacteria (GNBs), complicated urinary tract infections (CUTIs), extended-spectrum β-lactamases producing organisms (ESBL), carbapenem-resistant organisms (CRE/CRP), carbapenems, ceftazidime-avibactam, colistin, fosfomycin, *Enterobacteriaceae*

1. Introduction

Urinary tract infection is the second most common infectious presentation in community as well as in hospital settings. It has been estimated that 150 million people are diagnosed with

UTI each year worldwide [1]. It is mostly caused by GNBs. Over the past two decades, GNBs have developed complex mechanisms of resistance against most of the potent antibiotics. This has been a global challenge which has been identified by the World Health Organization as "one of the greatest threats to human health" [2]. This crisis is mostly man-made as it is attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry seeking better profitable agents.

This resulted in prolonged hospital stay, marked increases in the cost as well as increase in morbidity and mortality [3–6]. Furthermore, bloodstream infections associated with severe complicated urinary tract infections (CUTIs) are associated with high mortality rates of 20–50% among critically ill patients. Many urological procedures are complicated with such infectious manse, frustrating the surgeons and the patients [7].

Multiple mechanisms that enable the organism to become resistant include enzymatic transformation, modification of site of action, active efflux from the cell interior and, the prevention of entry of the molecules into the cell [8].

There are different confusing terminologies in addressing this process. An international panel of experts developed the following definitions: multidrug-resistant (MDROs) means acquiring nonsusceptibility to at least one agent in three or more antimicrobial categories, extensively drug-resistant (XDR) is nonsusceptible to at least one agent in all, but two or fewer antimicrobial categories, and pan-drug-resistant (PDR) isolates are nonsusceptible to any of the available antimicrobial classes [1, 9, 10].

The term "ESKAPE" was one of the former descriptions of pathogens that cause the majority of hospital infections while effectively "escaping" the effects of available therapeutics. Other terms include "SPICE organisms" which include many Gram-negative bacteria that have inducible, chromosomal AmpC β-lactamase genes. The resistance to antibiotics may not be detectable initially, but appears after a period of exposure to β-lactam antibiotics (during therapy or after).

We are focusing in this review on the most common and challenging groups of resistant Gram-negative organisms, the ESBL, and the CRE, as well as CRP. The other highly resistant organism, such as *Acinetobacter baumannii*, less frequently causes urinary tract infection and its therapy is even more complicated [11–13].

When treating these infections, clinicians have a few effective antimicrobials to choose from and many are associated with significant adverse effects. A critical step in managing these organisms is the early recognition and appropriate empiric therapy. Both showed morbidity and mortality benefits. In this chapter we will review the available data on managing UTIs caused by ESBL and the CRE/CRP.

2. Materials and methods

The purpose of this chapter is to review the available data on managing UTIs caused by resistant Gram-negative bacteria. Clinical trials and review articles (in English) were

identified from a Medline search (2000–2017), in addition to laboratory data and abstracts from international Conferences.

2.1. Definition: ESBL organisms

The term ESBL was originally applied to plasmid-encoded β-lactamases that are capable of inactivating extended-spectrum cephalosporins and are inhibited by β-lactamase inhibitors, such as clavulanic acid. *Enterobacteriaceae*, primarily *Escherichia coli* and *Klebsiella pneumoniae*, are among the most frequently producing bacteria [9].

ESBLs are plasmid-encoded or chromosomally encoded β-lactamases with broad activity against penicillins and cephalosporins. They are a diverse group of bacterial enzymes that break down and inactivate most β-lactam antibiotics. They are inhibited by the available β-lactamase inhibitors (clavulanic acid, sulbactam, avibactam, and tazobactam) and do not affect cephamycins (e.g., cefoxitin and cefotetan) or carbapenems. β-Lactamases are divided into A, B, C, and D classes according to their amino acid sequence homology (Ambler classification) [14].

These bacteria are usually multi-resistant, as they are frequently capable of resisting other antibiotics, such as the aminoglycosides, tetracyclines, and trimethoprim/sulfamethoxazole though other mechanisms, leaving few treatment options [3]. As these resistant genes are plasmid-mediated, they can be easily disseminated to other bacterial species [15–17]. UTIs caused by these organisms are seen at alarming rates in both hospital infection and in the community settings [15, 18, 19].

Although 95–100% ESBL organisms are still considered sensitive to carbapenems, rapid emergence of carbapenem resistance has been documented globally, and was linked to the over usage of these agents [20].

2.2. Epidemiology

Surveillance in Asia, Latin America, and Europe revealed dramatically increasing resistance to cephalosporins among *E. coli* and *Klebsiella* spp. [21]. In a large study in Turkey (SMART), the rate of ESBL in *E. coli* isolated from urine samples was high (50% hospital isolates and 38% community acquired isolates) [22, 23].

In one study, 21,414 positive urine cultures were collected from a University hospital in the UK. There were 1420 ESBL-positive specimens. There were a 44% increase, from 4.6 to 6.6%, of the ESBL-positive organisms over 2 years.

Multidrug resistance were detected in 75% of ESBL + *Klebsiella* spp. against >6 antibiotic classes [24].

In the CHINET surveillance system data from 2005 to 2014, ESBL production among *E. coli* isolates was between 51.7 and 55.8% [25].

The spreading of such isolates in the community is well documented, so containment of this type of bacterial infection will be real challenging [23]. There were many outbreaks caused by these organisms all over the globe with high morbidity and mortalities [17].

2.3. Risk factors

Many studies have implicated broad-spectrum cephalosporins as the major class associated with ESBL production; others considered fluoroquinolone and β-lactam-β-lactamase inhibitor combinations, as the main risk factors for ESBL infections [26]. Other risk factors include nursing home residence, diabetes, recurrent UTIs, male gender, prolonged hospitalization, intensive care admission, and urinary catheterization [19, 24, 27–29].

Prospective cohort study of 225 healthy German volunteers traveling to 53 different countries (mostly in Asia, Africa, and S. America) evaluated the risk of ESBL colonization. Stool samples were collected before and after traveling. The isolates were examined phenotypically and by PCR amplification sequencing. Among 191 participants that were ESBL-negative before travel, 30% were colonized by ESBL-producing *E. coli* after returning home [29, 30].

The use of antibiotics in farm animals as growth promoters is linked to this global disaster. In a recent study from India, 18 poultry farms were surveyed, 16 of them reported using antimicrobials for growth promotion. There were 1556 *E. coli* isolates, collected and tested. The prevalence of ESBL-positive strains in broiler farms was 87% [31]. Multiple studies have shown the benefit of early identifications of this organism, to offer the appropriate empiric therapy. A simple predicting score for early recognition was recently published. Four risk factors were identified; each was given a score of one. Scores above 2 had a sensitivity of (84%) and a specificity of (92%). These variables include recent antimicrobial use (OR, 15.29), recent invasive procedures (OR, 12.33), nursing home residents (OR, 27.77), and frequent emergency department visits (OR, 9.98) [32].

2.4. Mechanism of resistance

The most common mechanisms include enzymatic inactivation, target modification, reduced permeability, and active efflux. Antibiotic resistance can be intrinsic to specific microorganisms, which can be explained by their inherent characteristics. Point mutations on β-lactamase genes are responsible for emergence of ESBLs. These new genes could be transmitted through small mobile genetic element DNA (plasmid, transposons) to other bacteria from same or other species [5, 8].

A more distinct type of ESBL including CTX-M-type, AmpC, and carbapenemase, can confer phenotypic resistance that widens the resistance abilities against more antibiotics than the classical isolates [33].

2.5. Detection

These organisms are capable of resisting most of the third-generation cephalosporins but they are inhibited by clavulanate. This is the basis of detecting these organisms using routine laboratory tests such as double disk diffusion test or E-test. The size of zone of inhibition around one or more of the β-lactam-containing discs toward the clavulanic acid-containing disc is indicative of some ESBL producers [34, 35].

The detection of specific genes by PCR and sequencing are commonly used for final confirmation of ESBL producers. A commercially available multiplex real-time PCR can detect the predominant class A β-lactamase genes bla_{CTX-M}, bla_{SHV}, bla_{TEM}, and CIT-type AmpCs with high sensitivity and it is much faster than routine cultures [36].

2.6. Carbapenem resistant organisms

The carbapenems are the most potent agents with wide spectra of coverage. They are the most dependent agents in critical infectious syndromes. However, resistance to these agents has increasingly been reported worldwide, rendering them increasingly ineffective. These organisms are also capable of resisting other classes of antibiotics (aminoglycosides, fluoroquinolone, and co-trimoxazole), due to the frequent coexistence of other resistance genes on the same mobile genetic elements, rendering them superbugs. The most recent example is the emergence of colistin resistant genes in isolates which are already resistant to the carbapenems.

K. pneumoniae carbapenemase (KPC-class A) was the first CRE enzyme to be reported in 2001. New Delhi metallo-β-lactamase (NDM-class B) is one of the most recently reported metallo-enzymes. It has spread widely in the Indian sub-continent and now worldwide. The oxacillinase-48 type (OXA-48-class C) has been identified mostly in Mediterranean and southern European countries. Other mechanisms of resistance include efflux pump over activity (pumping the antibiotics out of the bacterial cell), hyper production of AmpC β-lactamase in the already highly resistant ESBL organisms, and changes in porin permeability [8].

Infections with such resistant isolates resulted in high morbidity, prolonged hospital stay, and mortality [37, 38]. In a pooled analysis of the 9 studies (985 patients), the mortality rate was higher among CRE-infected than carbapenem susceptible *Enterobacteriaceae*-infected patients (RR 2.05, 95% CI 1.56–2.69). The authors calculated 26–44% of deaths from 7 studies attributable to carbapenem resistance [39]. The rate was even higher (61%) in patients infected with KPC-expressing *K. pneumoniae* who received initially ineffective therapy [40].

2.7. Epidemiology

A multicenter observational study in 11 hospitals from 7 Latin American countries that included 255 patients with bacteremia was reported. Twenty-three percent of the isolates were CRE/CRP [38].

According to the latest data collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net), the rate of CRE rose from 6.2% in 2012 to 8.1% in 2015 [41].

CRE are more prevalent in Italy and Greece. In an active surveillance study, rectal swabs (and clinical samples) were collected from 15,104 hospitalized patients (over 2 years). *K. pneumoniae* CRE was detected in 496 consecutive non-replicated samples [42].

In a Greek study, 3449 *K. pneumoniae* isolates were recovered over 10 years. Among them, 1668 (48%) were CRE-producing. Sixteen percent of the isolates were resistant to colistin [43].

2.8. Detection

These include antimicrobial susceptibility testing, modified Hodge testing, and inhibitor-based testing. In 2015, the CDC-CRE surveillance definition was revised to one of two criteria: (1) resistance to any carbapenem according to current CLSI breakpoints (MIC ≥ 2 for ertapenem or ≥4 for doripenem, meropenem, or imipenem) or (2) demonstration of carbapenemase production. Several phenotypic assays are available commercially detecting carbapenemase production from bacterial culture within hours. The Carba NP test has high sensitivity and specificity that can differentiate between class A, B, and C CRE. In one study, its specificity and sensitivity were almost 96% [44].

There are many commercially available PCR-based testing for early recognition and confirmation.

2.9. Therapy of urinary tract infections caused by MDROs

2.9.1. ESBL-producing β-lactamases

In general and for serious life threatening infections, the carbapenems are the drugs of choice for infections caused by these organisms [12, 35]. However, the surge in using the carbapenems, resulted in the evolution of CRE/CRP, so there were multiple recent trials evaluating, carbapenem-sparing are regimens, mostly for less severe infections [12, 45–48].

2.9.2. CRE/CRP

In general, there is no clear consensus on managing these organisms. The available data are drawn from expert opinion or from small trials. There are few controlled trials that determined the best therapeutic so far [49, 50].

In the following sections, we will review the available data on different classes of antibiotics that have been used in managing ESBL, and then if applicable, will discuss their roles in treating CRE/CRP.

2.9.2.1. Carbapenems

They have a broad spectrum of antimicrobial activity more than any other classes of antimicrobials, and are potent bactericidal (ertapenem lakes anti-pseudomonas activities) [51–54].

In multiple non-randomized studies that included large number of patients with bacteremia, sepsis, and other serious infections, they showed high cure-improvement rates with great safety profile [54, 55].

Studies of the pharmacokinetic/pharmacodynamics data also showed superiority of this class of antibiotic in achieving the proper concentration above the bacterial minimal inhibitory concentrations (MICs) [56].

In vitro activities against many ESBL isolates are well documented against large collections of ESBL producing *Enterobacteriaceae* and *P. aeruginosa* isolates [57].

For treating CRE/CRP, limited data on combination regimens involving carbapenems (if MICs ≥ 8 mg/L) adding colistin or high-dose tigecycline or aminoglycoside or even triple combinations, seem to confer decent therapeutic advantage over monotherapy. For organisms with higher MIC, a combination of two or even three antibiotics may be needed.

In a recent meta-analysis of 22 studies of using, the most common regimen, carbapenems plus colistin or polymyxin had mortality advantages [38].

On the other hand, a retrospective study of 436 patients were recruited in the INCREMENT study-cohort (26 tertiary hospitals from 10 countries). The main outcome variable was 30 day all-cause mortality in patients with CRE/CRP bloodstream infection. Overall mortality was not different between those receiving combination therapy and monotherapy (35% vs. 41%) [58].

Synergy is another potential benefit arising from the use of antibiotic combinations.

Tigecycline with colistin, colistin with a carbapenem, fosfomycin with a carbapenem, fosfomycin with an aminoglycoside, and a carbapenem with an aminoglycoside have been reported as antibiotic combinations effectively administered to series of patients infected with carbapenemase-producing *Enterobacteriaceae* [4].

Efforts have been exerted to limit the usage of their precious agents by using alternative regimens whenever [46].

2.9.2.2. Piperacillin-tazobactam (PTZ)

PTZ is a broad-spectrum drug combination used in serious infections. However, the extensive usage of this agent accelerated the emergence of resistance [48, 59].

Some ESBL *E. coli* producers' isolates might have high in vitro susceptibility to PTZ; however, its clinical utility in serious UTIs, especially when associated with bacteremia, has been controversial. In a prospective, randomized, open-label comparison of the therapeutic efficacy of (PTZ), cefepime, and ertapenem in nosocomial UTIs with ESBL producers, 66 participants were evenly randomized to the PTZ and ertapenem treatment groups (cefepime arm was eliminated because of high treatment failure rate). The clinical and microbiological responses to both antibiotics were similar around 94% [60].

Similar non-inferiority of PTZ to carbapenems was shown in a retrospective analysis of bloodstream infection by an ESBL-producing organism, if susceptible in vitro [61].

In a post hoc analysis of patients with bloodstream infections due to ESBL producing isolates from 6 published prospective cohorts, the effect of amoxicillin-clavulanic acid, PTZ, and

carbapenems were compared. The mortality rates at day 30 were much higher with the first 2 antibiotics than with carbapenems [62].

In a retrospective observational study, 331 patients with ESBL bacteremias were evaluated. Empiric therapy with PTZ was used in 48% while 52% received carbapenems. The adjusted risk of death (14-day mortality) was 1.92 times higher for patients receiving empiric PTZ compared with carbapenem therapy (95% confidence interval, 1.07–3.45) [63].

In an editorial that tried to explain these controversial results, the authors mentioned various variables including the inoculum of the bacteria in the bloodstream, the sources of bacteremia (less fatal if from UTIs than central line infections), selection bias inherent to observational studies, and the presence of different genetic and virulence of the included bacteria [35].

A large recent multicenter randomized controlled open-label non-inferiority trial, MERINO trial, comparing meropenem (standard arm) against PTZ in adult patients with bacteremia caused by *E. coli* or *Klebsiella* spp., is ongoing, and hopefully, it will provide better answer to these conflicting data [61].

2.9.2.3. Cephalosporins

Cephalosporins have been less effective than comparative regimens in treating severe/serious infections with ESBL-producing bacteria. They are rapidly hydrolyzed by many ESBLs stains [60].

In many clinical studies, it was associated with a trend toward clinical and microbiological failure, as well as a trend of increased mortality [64, 65].

Despite their in vitro activities, there are reports of mutations and/or acquiring plasmids encoding AmpC-resistant genes during therapy with these agents. Others concerns about this agent failure include the decreased activity with high bacterial load (inoculum effect) and the failure to meet necessary pharmacodynamics targets due to inadequate dosing and/or interval schedules [50].

The most studied agent in this class is the cefepime. In the above-mentioned recent prospective, randomized, open-label that compared (PTZ), cefepime, and ertapenem in nosocomial UTIs, the microbiological and therapeutic efficacies of cefepime in febrile nosocomial urinary tract infection with ESBL *E. coli* were much less than the other competitors at 33% [60].

Data is more clear in patients with serious infections associated with ESBL-producing organisms' bloodstream infections. In a recent study, the mortality risk was 2.87 times higher for patients receiving cefepime compared with carbapenems (95% confidence interval (0.88–9.41) [66].

Another retrospective study included adult patients with BSI due to ESBL-producing *K. pneumoniae* or *E. coli*. In multivariate analysis, using cefepime as empirical therapy was associated with a trend toward an increased mortality risk, while empirical carbapenem therapy was associated with a trend toward decreased mortality [65].

There is few data from limited studies (with small number of participants) that showed cefepime is effective if used against in vitro susceptible ESBL-producing *Enterobacteriaceae* and as a de-escalation therapy in patients with uncomplicated UTIs [53, 67].

There are less robust data for the efficacy of other cephalosporins, cefmetazole (a cephamycins), in treating patients with extended-spectrum β-lactamase producing [68].

2.9.2.4. Aminoglycosides

Aminoglycosides are very potent antibiotics; however, their use is associated with significant renal and auditory toxicities. They have been successful in treating ESBL-UTIs as a monotherapy or in combinations with other agents. Combinations with other agents were effective in the treatment of CRE/CRP infections if the strain is susceptible to aminoglycosides [69].

Many of the plasmids that carry ESBL-producing genes also carry genes encodes resistant to aminoglycosides, mostly against tobramycin and gentamicin. In contrast, amikacin has retained high susceptibility rates, particularly against *E. coli.*

In a small study of UTI caused by highly resistant ESBL (also resistant to nitrofurantoin, fosfomycin, and quinolones and trimethoprim/sulfamethoxazole), amikacin intramuscular injections for 10 days achieved clinical success in 97.2%. Overall bacteriological success rate was 94.1% on the 7–10 days after treatment [70].

In a review of 20 studies evaluating CRE infections therapy, combination of aminoglycosides and carbapenems displayed the lowest mortality rate (11.1%) [71].

2.9.2.5. Fluoroquinolones

In many parts of the world, *E. coli* fluoroquinolone resistance rates are >20% among patients with community-acquired uncomplicated UTI and 50% among patients with complicated infections. The rate of resistance is even higher against *Klebsiella* spp. up to 70% in one recent international surveillance study [8, 72].

The co-existing of ESBL and fluoroquinolone resistant is extremely high in some areas of the world, in those who uses quinolones prophylaxis and in returned travelers to theses endemic areas [73]. Therefore, they are in general not recommended in the setting of high ESBL isolates [74].

Sitafloxacin is the newest member (fourth generation) of the fluoroquinolone family of antibiotics which has a broad-spectrum activity including many anaerobes [75]. In a recent prospective randomized controlled trial, comparing the clinical and bacteriological efficacy of sitafloxacin and ertapenem for non-bacteremic acute pyelonephritis caused by ESBL-EC was evaluated. Carbapenems were initially given to all patients, and then were randomized to one of the study drugs. The 2 arms were equal in the rates of clinical and microbiological cure [76].

These data suggest that fluoroquinolones may no longer be effective as first-line therapy for Gram-negative UTI in hospitalized patients and definitely in ESBL-producing organisms.

2.9.2.6. Trimethoprim/sulfamethoxazole

Although treatment with trimethoprim/sulfamethoxazole was traditionally effective in treating UTIS, the evolution of resistance is a current major concern. The Infectious Diseases Society of America guideline recommends against using it if local bacterial resistance rate is ≥20% [77]. Genes that encode for ESBLs are usually found on large plasmids accompanied by genetic determinants of resistance against multiple classes of antibiotics, such as aminoglycosides, sulfonamides, and fluoroquinolones. TMP-SMX is not recommended as an empiric treatment option of UTIs caused by resistant strains of *E. coli* or *K. pneumoniae* that reaches 40–66% in some areas in the world [78].

2.9.2.7. Tigecycline

Tigecycline has potent activity against a vast majority of organisms including Gram-negatives, Gram-positives, and anaerobes. It has almost susceptibility rates of 100% against ESBL-producing *E. coli*, however less potency against *K. pneumoniae* isolates producing. However, its use has concerning safety issues [11, 79]. Insufficient urinary excretion of the unchanged drug (15–22% of the dose) has prompted recommendations to avoid tigecycline for UTIs therapy [80, 81].

In a systematic review of the literature, 14 patients received tigecycline for UTIs caused by MDR Gram-negative bacilli. In 12 patients, there were initial microbiological clearance. Eleven patients had evidence of clinical response. However, there were post-therapy growth of tigecycline-resistant organisms in 2 cases [81].

Few studies tried to overcome this obstacle by using higher than the recommended dose for highly resistant organisms (initial dose of 200 mg one time followed by 100 mg every 24 h) [82].

The efficacy of tigecycline is further limited by increasing in vitro resistance in CRE. Serum and urinary levels of tigecycline are low, and most experts discourage the use of tigecycline as monotherapy for bloodstream or urinary tract infections [83].

This agent has no activity against *Pseudomonas*, *Proteus*, *Providencia*, and *Morganella.*

2.9.2.8. The polymyxins

The polymyxins are antibacterial agents that are produced from different strains of *Bacillus polymyxa*. Colistin and polymyxin B are available commercially; both have similar chemical structures and antibacterial activity in vitro, however they differ in their pharmacokinetic profiles. They can cause significant nephrotoxicity (reported in 20–60%) and neurotoxicity [69]. However, the spreading of extensively resistant Gram-negative bacteria as well as the paucity of newer effective antimicrobials let to the extensive usage of these agents as a last resort [84]. The vast majority of ESBL-producing *E. coli* and *K. pneumoniae* are susceptible to these drugs.

Currently, they are the backbone of most of the regimens used against the CRE/CRP organisms. Common combination regimens include tigecycline, carbapenem, minocycline, rifampicin, aminoglycosides, ampicillin/sulbactam, and piperacillin-tazobactam. Large clinical trials are underway to clarify the use of polymyxin different combinations [85].

Polymyxin B is administered directly as the active antibiotic, whereas colistin methanesulfonate is converted in vivo to colistin. The optimal dosing of these agents is still controversial.

Higher doses of colistin were proposed for managing serious CRE/CRP associated infections.

A recent systematic review that included 22 studies (observational studies as well as randomized controlled trials) of polymyxin-based combination therapy in adult patients with infections caused by CRE/CRP was published. The primary outcome was a 30-day mortality. Mortality was significantly higher with polymyxin monotherapy compared with combination therapy of polymyxin with tigecycline, aminoglycosides or fosfomycin, of 1.57 (95% CI = 1.06–2.32). However, the authors caution about the low quality of the evidence [86].

The mechanism of colistin resistance can be generally classified intrinsic or acquired by a recently recognized plasmid-mediated resistance gene [87].

In November 2015, plasmid-borne colistin resistance gene mcr-1 was initially identified in animal and clinical samples from China. As of September 2016, the mcr-1 gene was detected in 35 countries worldwide in human sources in 22 countries [88]. This created a real lethal superbug.

2.9.2.9. Fosfomycin (Fosf)

This agent has gained attention, as it has activities against both Gram-positive and Gram-negative MDR and XDR bacteria [89, 90–94]. It exhibits bactericidal activity against many Gram-positive and Gram-negative pathogens including many of the ESBL-producing *E. coli* and *K. pneumoniae* [91]. Fosf achieves very high concentrations within the urine and is therefore an excellent agent for cystitis, but it is not recommended for treating pyelonephritis or bacteremias due to inadequate concentrations in the blood. However, small studies have shown great results in using Fosf in complicated UTIs [95]. It is currently approved by the American Food and Drug Administration for the treatment of uncomplicated cystitis as a one-time dose of 3 g. Several studies have shown clinical efficacy in the treatment of ESBL cystitis when the dosing is extended to 3 g every 48–72 h for 3 doses [96].

A meta-analysis that evaluated the antimicrobial activity, or the clinical effectiveness of Fosf, reviewed 17 studies. Out of a total of 5057 clinical isolates of *Enterobacteriaceae*, 4448 were ESBL producers. Almost 90% of the isolates were susceptible to Fosf. Eighty percent of 748 *K. pneumoniae* isolates produced ESBL and were susceptible to Fosf [94].

In a prospective study of 47 patients with UTI caused by *E. coli*-ESBL-producing organisms, the outcome was evaluated. Fosfomycin was used in 27 patients and 20 patients received meropenem. The clinical and microbiological success was similar in 2 groups; however, the

costs were significantly lower in the Fosf group ($p < 0.001$). Fosfomycin was used orally 3 g sachet every other night total of 3 doses, while meropenem was used as a dose for 14 days [95].

In a retrospective study, 60 patients were treated for MDR UTI. There were cases infected with *Enterobacteriaceae*, *P. aeruginosa*, and *VRE*. The clinical response rate was 55%. Chronic kidney disease was associated clinical failure ($p = 0.04$) [92].

For the carbapenem-producing organisms, a very few clinical data on using this agent are available.

In Europe, an intravenous Fosf formulation is available. In a small (in 11 ICU patients) European study, intravenous Fosf (2–4 g q6 h) in combination with other antibiotics was associated with good bacteriological and clinical outcomes in all patients with carbapenem-resistant *K. pneumoniae* infections [96].

In an in vitro study, 365 isolates out of 2229 urine samples were evaluated. ESBL producers were detected in 65% were, 16% were carbapenem-resistant *Enterobacteriaceae*, almost 95% of the total isolates were susceptible to Fosf [97].

A recent, albeit pessimistic, data came from China. A study collected 233 clinical isolates CRE/CRP *Carbapenem Resistant Enterobacteriaceae/Carbapenem Resistant Pseudomonas* at four different hospitals. Forty-five percent of the strains (105/233) were resistant to Fosf. Plasmid-mediated fosfomycin-modifying enzymes fosA, fosA2, fosA3, and fosA5 genes were identified [98].

2.9.2.10. Nitrofurantoin

Another oral antimicrobial agent that can be considered for the treatment of ESB cystitis is nitrofurantoin. One study showed clinical cure rates of 69% in patients with ESBL cystitis in which all isolates were also resistant to SMX/TMP and ciprofloxacin [99].

Nitrofurantoin should only be used for lower UTI and should be avoided in patients with a creatinine clearance less than 60 (few studies accepted GFR more than 40) mL/min as reduced renal function results in decreased active drug within the urine [100]. It is contraindicated in pregnancy.

2.9.2.11. Cefoperazone-sulbactam

In a larger in vitro study, against the GNBs, a total of 18,386 organisms including 13,224 *Enterobacteriaceae* and 3536 *Pseudomonas* were collected (2013–2014) as part of the SENTRY Antimicrobial Surveillance Program. Cefoperazone/sulbactam inhibited 94% of *Enterobacteriaceae* [101]. There are limited clinical data on the usefulness of this agent against ESBL or CRE/CRP organisms in the urinary tract.

2.9.2.12. Ceftazidime-avibactam (Cef-Avb)

Ceftazidime, a third-generation cephalosporin, when combined with avibactam has potent activities against β-lactamase-producing Gram-negative pathogens including ESBL, AmpC

β-lactamases, and *CRE.* Currently, Cef-Avb is approved for complicated UTIs (limited to patients without other treatment options in the empiric and documented treatment of MDROs).

In an in vitro study, it was tested against collection of international urinary isolates (1797 isolates were collected from 159 medical centers). All ESBL isolates as well as meropenem-non-susceptible *E. coli* and *K. pneumoniae* isolates were susceptible to Cef-Avb [102].

In another study, 34,062 isolates of *Enterobacteriaceae* from patients (with mostly UTIs) were collected (International Network for Optimal Resistance Monitoring, surveillance from 39 countries). Overall, 99.5% of isolates were susceptible to Cef-Avb. It was also active (99.9%) against molecularly confirmed ESBL-producing, plasmid-mediated AmpC-producing (100%), and ESBL- and AmpC-producing (100%). It lacks activity against the metallo-β-lactamase producers (NDM-1 enzyme) [103].

The REPRISE, an international, randomized, open-label trial, recruited 333 patients from 16 countries worldwide. The study recruited patients mostly with complicated UTIs caused by ceftazidime-resistant *Enterobacteriaceae* or *P. aeruginosa*. They were randomly assigned, 165 to Cef-Avb and 168 to best available therapy. The overall proportions of patients with a clinical cure were similar in the 2 arms [104].

In another clinical study, Cef-Avb was compared to imipenem-cilastatin in hospitalized adults with serious complicated UTI due to Gram-negative pathogens. Patients were allowed to switch to oral ciprofloxacin after at least 4 days on the study drug. Patients in the Cef-Avb group had a better microbiological response (70% vs. 71%) [105].

The RECAPTURE study recruited 033 patients, who were randomized in 2 arms, 393 received Cef-Avb and 417 received doripenem, with possible oral antibiotic switch (total duration was 10–14 days). Combined symptomatic resolution/microbiological were similar in the 2 arms (70.2% vs. 66.2%, respectively) [106].

In a recent study, the outcome of therapy with ceftazidime-avibactam (38 patients) was compared to the outcome of therapy with colistin (99 patients) with CRE infections. Most patients received additional anti-CRE agents as part of their treatment. All-cause hospital mortality at 30 days and after were 9% vs. 32%, respectively [107].

Salvage therapy: in a case series of 36 patients, mostly with life-threatening infections received Cef-Avb as a salvage therapy. The causative organisms were CRE (2 were CRP). In 65.8% of patients, other concurrent antibiotics were used. More than 70% of the patients experienced clinical and/or microbiological cure [108].

Resistance: in less than 2 years since its approval, resistant strains have been isolated. Cef-Avb-resistant *K. pneumoniae* emerged in 3 patients after using Cef-Avb for 10–19 days [109].

2.9.2.13. Ceftolozane-tazobactam (Cef-Taz)

This agent was approved in 2015 for the treatment of complicated urinary tract infections (adults with limited or no other therapeutic options) [110]. There are many in vitro studies that

demonstrated activity against Gram-negative and Gram-positive microorganisms, including *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa* as well as coverage of most ESBL-producing organisms and some anaerobes [110, 111].

Cef-Taz was tested in vitro against 3851 *P. aeruginosa* isolates collected from 32 U.S. hospitals. It was active against 97.0% of the isolates, which was better than 7 other broad spectra antibiotics. A total of 363 isolates were classified as extensively drug resistant; Cef-Taz was active against 76.9% of these isolates [112].

The ASPECT is a randomized, double-blind, double-dummy, non-inferiority trial over 25 countries. 1083 patients enrolled, of whom 82% had pyelonephritis. Patients were randomly assigned to receive Cef-Taz or intravenous high-dose levofloxacin for 7 days. Overall, the composite cure rates were higher in the Cef-Taz group than in the levofloxacin. In a subgroup analysis, clinical cure was seen in 90% compared with 73% in patients with ESBL-producing uropathogens [113].

2.9.2.14. Ceftaroline/avibactam

Ceftaroline is a cephalosporin with broad-spectrum activity against Gram-positive and Gram-negative organisms. When Ceftaroline combined with avibactam, it gains activities against many ESBL-producing organisms in vitro. It was tested in one study against 272 ESBL *Enterobacteriaceae* strains. All isolates were inhibited by ceftaroline-avibactam at ≤4 μg/mL; however, it exhibited limited activity against *Acinetobacter* spp. and *P. aeruginosa* [114].

There are no clinical studies that tested the activity of this agent on UTIs caused by any MDROs.

2.9.2.15. Ceftriaxone + sulbactam + disodium edetate (Elores)

It is a novel molecule, which combines β-lactam plus β-lactamase inhibitor. It has shown activities against many resistant Gram-negative bacterial infections. There is a limited data on its spectrum, usage (mostly in India), and its role in urinary tract infections in specific.

In one study, Elores activity was compared to other comparators (including carbapenems) in treating various infectious syndromes. There were 2500 patients enrolled in the study, in which 24% of the patients had UTIs (no specifics on severity or the causative organisms). The clinical cure/improvement was achieved in 98%. There was no clear description on the types or the incidence of resistant organisms in the study [115].

2.10. ESBL and CRE urinary tract infections with pregnancy

Few studies have been conducted regarding the prevalence of ESBL-producing organisms in pregnant women. In Ireland, a low figure of 1.63% of pregnant patients was colonized with ESBL organisms (perianal). Similar rates were seen in a Norwegian study (2.9%) [116].

Higher rates have been reported in other countries: 5.4% in Argentina and 15% in India [117]. In India, 47% in *E. coli*-related UTIs in pregnant patients were ESBL-producing *E. coli* [117–119].

Peripartum maternal transmission of ESBL organism to newborn infants was documented [120].

Recently, first outbreak of a CTX-M ESBL-producing *E. coli* in an Irish neonatal intensive care unit was reported. This outbreak was mediated by mother to neonate transmission [121].

Carbapenem are the drugs of choice for treating complicated UTIs and pyelonephritis due to ESBL pathogens in pregnancy [122]. In small studies, orally administered fosfomycin have been used to treat cystitis with ESBL pathogens with good success.

A case control study compared outcomes in pregnant women with ESBL-UTIs. Suboptimal treatment was noted in the majority of cases involving ESBL-UTIs (89%, n = 40), which was far more likely than what was observed for non-ESBL infections. Data support the importance of more aggressive treatment and follow-up of pregnant women with ESBL-UTIs to prevent secondary clinical pyelonephritis [123].

There are very limited data on CRE/CRP UTI in pregnancy. A case report of community-acquired pyelonephritis caused by KPC-producing isolate was reported in Australia [124].

Authors were refrained from using colistin, because of its toxicity in pregnancy (category C). Tigecycline was not considered either (category D). Rather, they added cefepime, which is regarded as safe in pregnancy (category B) and offers potential synergistic activity with fosfomycin, which is also an inhibitor of cell wall synthesis. In that study, the isolate was resistant to cefepime in vitro. By using 6 g/day as a continuous infusion, they estimated that levels in plasma of 20–30 μg/mL were maintained; moreover, cefepime achieved a very high concentration in the urine. Therefore, it has been reasoned that concentrations of cefepime sufficient to inhibit the growth of *K. pneumoniae* (MIC >32 μg/mL) would be maintained in the urine and genitourinary tract. This approach was successful, as proven by sterile urine cultures (obtained weekly while the patient was on cefepime and 6 weeks after the end of therapy) and the absence of symptoms.

For these challenging cases, a new drug (see above), ceftazidime-avibactam, has shown great activities against most of the ESBL and many of the CRE/CRP organisms. This novel agent is safe during pregnancy. However, there are no randomized trials to show this activity, and it should be considered as a salvage therapy [125].

2.11. Duration of therapy

The optimal length of treatment UTI with highly resistant organisms has not been extensively studied. As there are many different causes of underlying abnormality, a simple recommendation cannot be made. 10 to 14 days of antibiotics are usually recommended for patients with bacteremia, hypotension, and other signs of severe sepsis. Recent clinical trials included

complicated urinary tract infections with resistant organisms that have used the study drugs for 10–14 days [93, 105, 106].

2.12. Infection-control

A successful infection program should be able to recognize, screen, and isolate both colonized and infected patients. Standard and transmission-based precautions are strictly applied at all times. Other basic measures including hand hygiene, use of personal protective barriers, and aggressive environmental cleaning are very beneficial. Implementation of simple items-bundles (multiple-drug resistant bundles MDROs) have shown to be very effective in controlling outbreaks.

Hospital-wide vs. high risk areas (ICU, dialysis centers) (routine vs. on outbreaks based) and clinical and bacteriological surveillance have been useful in early identifications and isolation of index cases. The use of molecular technologies including polymerase chain reaction (PCR) optimized the surveillance process [14].

A strict protocol including the above-mentioned interventions showed a great success in reducing the nosocomial spreading of the highly resistant organisms. During the intervention, nosocomial CRE acquisition in acute care declined from a monthly high of 55.5 to an annual low of 4.8 cases per 100,000 patient-days ($p < 0.001$) [126].

2.13. Antimicrobial stewardship

Multidisciplinary program including physicians, pharmacists, and microbiologists that aims to control the usage of antimicrobial is mandatory. In one study, carbapenem use was strictly restricted through antimicrobial stewardship in an effort to control MDROs spreading in an ICU setting. The study protocol also included strict environmental cleaning and disinfection in addition to basic infection control measures. The rate of hospital acquired MDRO *Acinetobacter* decreased from 22.82 cases per 1000 patient-days to 2.68 cases per 1000 patient-days after the protocol implementation ($p < 0.001$) [127].

2.14. Summary of recommended therapy

2.14.1. ESBL producing organisms

In general, carbapenems are the most reliable treatment for infections caused by ESBL-producing bacteria. As shown above, the over usage of these agents resulted in the emergence of the CRE. Multiple trials have shown other effective-carbapenem sparing regimens.

We proposed the following:

A. Uncomplicated cystitis caused by ESBL producing *E. coli* and without any indwelling catheters or obstruent: fosfomycin would be effective (and approved) therapy. In cystitis caused by other ESBL producing organism, fosfomycin alone was associated with significant clinical and microbiological failures.

On the other hand, our (and others) clinical exercise with monotherapy and single dose of fosfomycin was also associated with high rates of relapse. We also have great concerns about the rapid progression of fosfomycin resistance. This will require further research.

Meanwhile, we are proposing fosfomycin 3 g oral sachets twice a week for 3–4 doses with nitrofurantoin 100 mg twice a day for 10 days (if susceptible).

B. For complicated UTIs: monotherapy with carbapenems, piperacillin-tazobactam, aminoglycosides or ceftazidime-avibactam would be effective.

2.14.2. CRE/CRP producing organisms

Treatment of carbapenem-resistant organisms is a real challenge because of limited choices for effective reliable regimens. There are no randomized controlled trials evaluating different antibiotic options for carbapenemase producers. There are many observational studies; combination therapy appears to be superior to single-drug therapy. Combinations of a polymyxin, tigecycline, and meropenem have met with the greatest success. Meropenem has been used in these combinations despite a lack of in vitro susceptibility. Recently ceftazidime-avibactam is showing promising results. It has good activity against (nearly) all class A and class C β-lactamases as well as OXA-48 carbapenemases. However, it lacks activity against the metallo enzymes.

If we can summarize the data above:

2.15. For complicated UTIs/critically ill patients

1. Aminoglycosides (amikacin or gentamicin) or colistin.

Plus: a carbapenem or

2. Ceftazidime-avibactam (single agent).

3. Tigecycline plus colistin or aminoglycosides: have been tried in few trials.

4. Triple combinations including aminoglycoside, carbapenem, colistin, rifampicin, tigecycline, and fosfomycin have demonstrated synergistic or bactericidal effects in few small studies.

Even with the above-mentioned regimens, failure of therapy is very common, as tigecycline and polymyxin do not have good clearance in the urine.

3. Conclusion

The rapid and global spread of antimicrobial-resistant organisms in recent years is a global challenge. The overuse of antimicrobial use in humans and animals coupled with increased

global connectivity facilitated the transmission of Gram-negative infections harboring extended-spectrum β-lactamases. When treating these infections, clinicians have a few effective antimicrobials to choose from and many are associated with significant adverse effects. Definitive therapy should always be guided by susceptibility testing. Expert consultation with an infectious disease specialist is recommended.

Declaration of interest

The authors report no conflicts of interest.

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Urinary tract infection (UTI) is a problem so common and so significant in routine clinical practice that accurate diagnostics are especially important. In particular, complicated UTI is associated with an increased rate of therapy failures, as a result of possible biofilm formation on foreign elements and antibiotic resistance, as well as the increased possibility of an infection recurrence. These are the arguments for the constant search for novel diagnostic tools and techniques. These and many other vital topics regarding UTI complications, management, and treatment, in addition to antibiotic resistance and bacterial virulence traits allowing us to mitigate or avoid antibiotic action, are presented in this book.

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