Review artiche

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Urinary tract infection in chronic kidney disease patients

Infección del tracto urinario en la enfermedad renal crónica

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Abstract

Infections in chronic kidney disease patients are a major cause of morbidity and mortality. Renal patients have specific risk factors for acquiring infections, which also tend to be more severe and have a more rapid progression and slower resolution than in the healthy individuals. Urinary tract infection in renal patients is often complicated due to the presence of diabetes, multiresistant microorganisms, anatomic or functional abnormalities of the urinary tract, metabolic disturbances and the frequent use of urinary catheters. It causes one of the highest rates of hospitalization among dialysis patients and is highly prevalent in kidney transplantation. The aim of this work is to review the etiology, microbiological diagnosis and treatment of urinary tract infections in chronic kidney disease patients.

Key words: Urinary tract infections, chronic kidney disease, renal replacement therapy, dialysis, kidney transplantation, hospitalization.

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Resumen

Las infecciones en personas con enfermedad renal crónica son una causa importante de morbimortalidad. Los pacientes renales presentan factores de riesgo específicos para la adquisición de infecciones, que además suelen ser más graves, de progresión más rápida y de resolución más lenta que en sujetos sanos. La infección del tracto urinario en esta población es a menudo complicada debido a la presencia de diabetes, microorganismos multirresistentes, anomalías anatómicas o funcionales del tracto urinario, alteraciones metabólicas y el uso frecuente de sonda vesical. Las infecciones urinarias ocasionan una de las tasas más altas de hospitalización en diálisis y son muy prevalentes en el trasplante renal. Este trabajo tiene como objetivo revisar la literatura publicada sobre la etiología, el diagnóstico microbiológico y el tratamiento de las infecciones del tracto urinario en pacientes con enfermedad renal crónica.

Palabras clave: infecciones urinarias, insuficiencia renal crónica, terapia de reemplazo renal, diálisis, trasplante de riñón, hospitalización.

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Introduction

Urinary tract infection (UTI) includes a heterogeneous group of processes with a variable clinical symptomatology. Its incidence in the population has changed in the last decade, with an increase in the prevalence of community-based UTI, among other reasons due to the increase in life expectancy, while the prevalence of nosocomial UTI has decreased significantly, due to the reduced use of urinary catheters and the replacement of open circuits with closed ones.[1]

Chronic kidney disease (CKD) is defined as the presence for at least three months of an estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m^2 or the existence of kidney injury, defined by the presence of structural (detected by ultrasound) or functional (presence of albuminuria or alterations of the urinary sediment or electrolyte secondary to glomerular, vascular or tubulointerstitial damage) renal abnormalities.[2]

Infectious complications in CKD constitute an important source of morbidity and mortality, especially in patients undergoing renal replacement therapy (RRT), either hemodialysis, peritoneal dialysis or kidney transplantation, presenting an infectious process with a three-fold higher frequency.[3-7] The occurrence of infections in CKD is independently associated with progression to end-stage CKD, cardiovascular ischemia, congestive heart failure, and mortality.[8]

The patient with CKD has more often risk factors for acquiring different infections. On the one hand, uremia causes alterations in the humoral response, the lymphocyte function, the macrophages and the polymorphonuclear cells. On the other hand, the underlying cause of CKD is sometimes a condition that compromises the normal voiding of urine and the integrity of the urinary tract, or implies its manipulation (vesicoureteral reflux, neurogenic bladder, urethral valves, prostatism, bladder catheterization, renal catheterization, complicated lithiasis, polycystosis). In other cases, diabetes is the underlying cause of both CKD and the greater susceptibility to the appearance of UTI and its worse evolution, especially in elderly and female patients.

The incidence of UTI in CKD increases as the disease progresses and the defense mechanisms against the infection become deteriorated.[9] In patients on dialysis they are responsible for high hospitalization rates, followed only by lung infection and sepsis.[4] In the case of kidney transplant recipients, bacteriuria is even more frequent (35-80%) as well as its progression to UTI due to previous infections in the transplanted kidney, manipulation of the urinary tract and immunosuppressive medication.[10] The occurrence of UTI is the first cause of bacteremia in these patients and implies an increased risk for emergence of renal failure and graft failure.[11]

Despite the undoubted increase in the number of patients with CKD in recent years, there are few publications on UTI in this population, in which the antibiotic treatment is also an especially problematic issue, since it entails the risk of nephrotoxicity and the need for pharmacological adjustment to renal function or dialysis; the low pH in the urinary medium and the endothelial alterations in turn tend to reduce the effectiveness of the treatments.

The objective of this review is to offer a complete, practical and updated view on the particularities of the management of complicated and uncomplicated UTI in patients with CKD.

Classification of UTI

According to their anatomical location, urinary infections are classified as: 1) lower tract infections: urethritis, cystitis, prostatitis, and epididymo-orchitis; and 2) of the upper urinary tract: acute pyelonephritis, intrarenal abscess, perinephric abscess and infectious papillary necrosis. The first group is more frequent and is triggered via ascending route, while the second group can originate both by ascending route and hematogenous route (bacteremia). Although the symptomatic location of the UTI is defined at a certain level, all the tissues of the urinary tract can be partially affected. The symptomatology, the prognosis, and the therapeutic guidelines are different in each clinical situation.

Asymptomatic bacteriuria is defined by the presence of more than 100,000 CFU/ml in two urine

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samples in the absence of clinical symptoms, although it is accompanied by overt leukocyturia in the majority of diabetic and elderly patients. In general, asymptomatic bacteriuria does not require treatment, except in the following cases, in which its systematic detection is recommended: pregnant women (if not treated, it can lead to pyelonephritis in 20-40% of cases),[12] children under 5 years of age (especially if they present vesicoureteral reflux), patients undergoing manipulation of the urinary tract (risk of bacteremia), neutropenic patients (risk of sepsis) and kidney transplant recipients (per protocol in the first 3-6 months after transplantation due to the risk of sepsis and graft failure).[13]

It is considered an **uncomplicated UTI** the one which affects individuals with a structurally normal urinary tract and whose defense mechanisms are intact. The majority of these infections respond well to antibiotic treatment. Cystitis is characterized by dysuria, frequency of urination and imperious mictional urge (voiding syndrome), often accompanied by suprapubic pain, bad-smelling urine and hematuria; in women –and especially in elderly women- urinary incontinence is relatively frequent. In women with voiding syndrome, the differential diagnosis of cystitis with infectious or traumatic urethritis and with vaginitis can be considered; in young or middle-aged men with voiding syndrome and absence of urological pathology or manipulation of the urinary tract, urethritis should be ruled out, especially if there is urethral suppuration, or prostatitis, if the infection is recurrent.

We talk about **complicated UTI** when it affects patients with anatomical or functional abnormalities of the urinary tract, urinary tract instrumentation, indwelling urinary catheter, CKD, diabetes, metabolic abnormalities, immunosuppression, or the presence of multi-resistant microorganisms (Table 1). Diabetic patients are more susceptible to the progression of the infection to the renal parenchyma, especially in UTI due to enterobacteria[14] and when there are associated risk factors such as advanced age, proteinuria, low body mass index, CKD, autonomic neuropathy and a history of recurrent UTI.[15] Early diagnosis and adequate treatment are essential to avoid complications that cause the deterioration of kidney function.[16,17]

Acute pyelonephritis should be suspected in the presence of fever, chills, impaired general condition, low back pain or positive fist percussion; and with less frequency, nausea or vomiting. Around 30% of patients with cystitis suffer from silent infection of the renal parenchyma, especially men and pregnant women, children under 5 years of age, diabetics, immunosuppressed individuals, patients with CKD, anatomical or functional abnormality of the urinary tract or UTI due to *Proteus*. Acute pyelonephritis usually presents with leukocytosis with a left shift and bacteremia in 20-30% of cases, of which one third results in septic shock. Kidney function can be impaired by sepsis, endotoxemia, hypotension, and renal hypoperfusion.[18]

Chronic pyelonephritis arises in patients with significant anatomic alterations, such as obstructive

Table 1. Factors that define a complicated UTI.

Structural abnormalities
Urinary tract obstruction, prostatitis, renoureteral lithiasis, urinary diversion procedures, renal cyst infection, urinary catheters, bladder catheter, vesicoureteral reflux, neurogenic bladder, renal abscess, urinary tract fistulas
Metabolic abnormalities
Diabetes, pregnancy, kidney failure
Immunity alterations
Solid organ transplantation, neutropenia, congenital or acquired immunodeficiencies
Unusual or multidrug-resistant pathogens
Fungi, *Mycoplasma*, *Pseudomonas aeruginosa* and other resistant bacteria, producers of ESBL and carbapenemases, stone-forming bacteria (*Proteus*, *Corynebacterium urealyticum*).

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uropathy, struvite stones or, more frequently, vesicoureteral reflux, which occurs in 30-45% of children with symptomatic infections.[19] This chronic, patchy and often bilateral infection of the kidneys produces calyceal atrophy and deformation, with scarring of the overlying parenchyma, and constitutes, together with chronic interstitial nephritis and proportionally to increasing age, the etiology of end-stage CKD in 11-28.6% of patients under RRT with dialysis or kidney transplantation, according to the most recent data available from the Spanish Registry of Renal Patients.[20]

Microbial etiology of UTI in CKD

The pathogenic microorganisms that can cause UTI are very varied and come from all levels of the biological kingdom: bacteria, fungi, viruses and parasites.

The infection is bacterial and monomicrobial in more than 95% of cases; the rest are found in hospitalized, instrumentalized or surgically intervended patients for urological pathology, with neurogenic bladder and/or permanent urinary catheter bearers.[21]

The etiology of UTI varies depending on the type of infection, the existence of predisposing factors, previous antimicrobial treatments, and the acquisition context (community or nosocomial). Most episodes are produced by microorganisms that come from the colon and, therefore, the fecal microbiota of the patient conditions to a great extent the etiology of the UTI; the rest have an exogenous etiology, due to microorganisms introduced into the urinary tract during its manipulation. Acute pyelonephritis of hematogenous origin is rare and is usually produced by *Staphylococcus aureus* and yeasts.

UTI in CKD patients has a microbial etiology similar to that of the rest of the population, with a predominance of gram-negative bacilli over gram-positive cocci.[22] However, the frequency of gram-positive cocci and yeasts in the UTI of patients with CKD is much higher than in the general population. As a reference, in a review of 21,083 positive urine cultures of patients from the Puerta del Mar de Cádiz University Hospital (Spain), we found 24.9% of UTIs due to gram-positive cocci and 6% due to yeasts in patients with CKD in relation to 7.9% and 1.7% in the general population, respectively (Table 2). Another important fact is that the frequency of mixed infections and by microorganisms resistant to conventional antimicrobials increases in patients with CKD.[22] In the case of our series, we found 6.4% of strains of extended spectrum beta lactamases (ESBL) producing *Escherichia coli* and 7.3 and 9.1% of ESBL and carbepenemases producing *Klebsiella pneumoniae* respectively.

Escherichia coli is the microorganism most frequently implied in any type of patient, both in the hospital and out-of hospital settings, and in complicated and uncomplicated UTI.[23,24] Its frequency is lower in treated patients and in chronic infections, at the expense of other opportunistic microorganisms in the presence of comorbidity, antibiotic therapy, immunosuppression, urological instrumentation and surgical maneuvers. The existence of colonization factors, such as pili or fimbriae in *E. coli*, with high affinity for P1 glycosphingolipids of the cells of the urethral epithelium, gives it greater adherence and rapid invasion of the urinary tract, although not all strains have the same ability to infect the urinary system. Four phylogenetic groups have been identified in *E. coli*, which are referred to as A, B1, B2 and D. Extraintestinal pathogenic *E. coli* strains, including the uropathogenic ones, derive mainly from the B2 group and to a lesser extent from the D group and harbor genes encoding extraintestinal virulence factors. The isolates of *E. coli* of the B2 group cause 69% of cystitis, 67% of pyelonephritis and 72% of urinary sepsis.[24]

In patients with CKD, there is an increased frequency of UTI produced by other gram-negative bacilli of the group of enterobacteriacea different from *E. coli*, such as *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Morganella morganii* and *Citrobacter freundii*, together with *Pseudomonas aeruginosa*, generally present in patients bearers of Foley catheters and in complicated infections. In the abovementioned series we have observed a higher proportion of UTIs caused by *Proteus mirabilis* in

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Table 2. Microbial etiology of UTI in CKD vs. without CKD.

Microorganisms	699 patients with CKD		20,384 patients without CKD	
	Number	Percentage (%)	Number	Percentage (%)
Escherichia coli	296	42,35	13.123	64,38
Klebsiella pneumoniae	55	7,87	1.554	7,62
Pseudomonas aeruginosa	46	6,58	1.017	4,99
Proteus mirabilis	28	4,01	1.628	7,99
Enterobacter cloacae	25	3,58	278	1,36
Morganella morganii	14	2	292	1,43
Enterobacter aerogenes	6	0,86	227	1,11
Acinetobacter baumannii	6	0,86	211	1,03
Citrobacter freundii	5	0,72	3	0,01
Serratia marcescens	2	0,29	94	0,46
Total Gram-Negative bacilli	483	69,1	18.427	90,4
Enterococcus faecalis	89	12,73	1.042	5,11
Enterococcus faecium	26	3,72	26	0,13
Staphylococcus epidermidis	24	3,43	166	0,81
Streptococcus agalactiae	14	2	159	0,78
Staphylococcus aureus	9	1,29	123	0,6
Staphylococcus saprophyticus	7	1	85	0,42
Staphylococcus coagulase (-)	5	0,72	16	0,08
Total Gram-Positive cocci	174	24,89	1.617	7,93
Candida albicans	36	5,15	300	1,47
Candida glabrata	4	0,57	28	0,14
Candida parapsilosis	2	0,29	12	0,06
Total yeasts	42	6,01	340	1,67

*Data from the Puerta del Mar University Hospital, Cádiz.

the general population and a slight predominance of *Enterobacter aerogenes*, *Acinetobacter baumannii* and *Serratia marcescens*. Regarding the gram-positive cocci, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus agalactiae* and the various species of *Staphylococcus* constitute, in CKD patients, the etiology of the UTI not caused by gram-negative bacilli, with a frequency clearly higher than in the general population.[25] The same happens with yeasts, especially with the *Candida albicans* species, responsible for ITUs in immunosuppressed patients, even more in diabetics and in those who have indwelling catheters.[26]

E. coli and *Klebsiella pneumoniae* strains that produce extended spectrum beta-lactamases (ESBL) and carbapenemases deserve a special mention. Resistance to carbapenems may be due to the production of carbapenemases or of enzymes that alter the action of carbapenems in association with other mechanisms such as alterations in the permeability of the wall of the strain, due to modifications in its porins.[27,28] CKD patients more frequently have one or more risk factors for developing infections with ESBL (+) strains, such as diabetes, the use of urinary or vascular catheters, hemodialysis treatment and the previous use of

broad-spectrum cephalosporins and quinolones.[29] In addition, ESBL-producing strains are often resistant to other groups of antimicrobials, including aminoglycosides and fluoroquinolones, further limiting treatment options.[30]

Diagnosis of UTI

The diagnosis of UTI is usually established by the symptoms and the presence of leukocytes, nitrites, leukocyte esterase and bacteria in the urinary sediment. Even though the guidelines do not recommend this method in the general population except in doubtful cases, symptomatic recurrence, or limited therapeutic options due to intolerance or allergies to antibiotics,[31] in the population with CKD, this suspicion should be confirmed, if possible, by the demonstration of the etiologic agent by urine culture,[32] given the higher risk of multidrug resistance in this population.

Urine culture. The urine culture is a method of study of the UTI that has not been superseded by automated techniques. It is essential to distinguish an accidental contamination from significant bacteriuria. It is performed taking into account the urinary sediment and/or the Gram stain of a drop of non-centrifuged urine.

Urine culture is aimed at the isolation of the highest number of microorganisms with the lower number of culture media; the use of at least two plates is recommended: one of blood agar or chocolate agar, for the quantitative estimation of the bacteriuria by means of the colony count, and another of a lactose selective agar (MacConkey agar), for the differentiation of enterobacteria and other gram-negative bacilli.

Most UTIs have bacterial counts equal to or greater than 100,000 CFU/ml, but 20% have counts between 1,000 and 100,000 CFU/ml.[33] The quantitative appreciation of the bacteriuria is subject to numerous circumstantial factors: collection of the urine, physicochemical conditions thereof, speed of the exam, presence of labile microorganisms, and the circumstances of the patient and the infection. The following situations can be considered:

- In urine obtained by suprapubic puncture or nephrostomy, any count is indicative of infection.
- Bacteriuria between 1,000 and 10,000 CFU/ml suggests contamination, especially if it is of mixed flora. Some microorganisms, such as *Staphylococcus* and *Candida*, should be assessed with low counts.
- If there are between 10,000 and 100,000 CFU/ml of a single microorganism, a UTI should be suspected. The repetition of the culture, the presence of leukocyturia and the symptoms help to the correct interpretation. A repeated culture with more than 50,000 CFU/ml of the same organism confirms the UTI.
- Counts equal to or higher than 100,000 CFU/ml are indicative of UTI. Mixed infections are rare and are generally the result of inadequate sample collection, except in patients with indwelling catheters or anatomical abnormalities.

The urine culture may be negative or of doubtful assessment in the following cases: UTI due to microorganisms with culture exigencies, presence of L-forms, prostatitis, urethritis, chronic and recurrent pyelonephritis, urinary obstruction due to lithiasis, increased diuresis, recent previous urination and presence of antimicrobials in the urine.

Diagnosis of UTI in patients with CKD. As mentioned, patients with CKD at any stage, as well as those with kidney transplants, present different degrees of immunosuppression that make it necessary to be alert about the possible appearance of a complicated UTI. In the case of a UTI with fever, it is necessary to rule out the elevation of acute phase reactants, such as C-reactive protein and erythrocyte sedimentation rate, as additional data of severity and markers of evolution. However, the absence of a febrile response in patients on RRT and kidney transplant recipients is not uncommon, therefore, given the affectation of the general condition; such determinations should be made in this group of patients.

Unlike the general population, in which the hyperechogenicity of the parenchyma studied by

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renal ultrasound may be a finding suggestive of its involvement with the development of pyelonephritis, patients with CKD present this abnormality at baseline, so its appearance will not mean the development of this complication in the absence of other data thereof. Even so, the technique may be useful in suspected UTI complicated by renal abscess, xanthogranulomatous pyelonephritis, emphysematous pyelonephritis, coraliform lithiasis, and urinary tract obstruction.

Additionally, the following particularities of the diagnosis of UTI in patients with CKD must be taken into account:

- The prevalence of diabetes is high in the population with CKD and the symptoms may be scarce when it is present.
- Patients on hemodialysis are often anuric, so the symptoms can be reduced to suprapubic pain. Likewise, the presence of UTI should be suspected in an anuric patient on hemodialysis who suddenly recovers spontaneous voiding.
- In peritoneal dialysis, the diagnosis of UTI must be accompanied by a vigilant attitude regarding the eventual appearance of peritonitis as a complication thereof.

Treatment of UTI in CKD

The treatment of UTI is based on two fundamental pillars: adequate patient instruction and bacteriological surveillance. Besides prescribing antimicrobials, measures to prevent UTI should be established: adequate water intake, frequent urination, complete emptying of the bladder (abdominal press), hygienic measures after defecation and antibiotic prophylaxis prior to manipulation (cystography, flowmetry, urethral dilation, double J replacement, etc.).

In antimicrobial treatment, it is necessary to consider the etiological variability and the circumstances that predispose to infection, as well as the different clinical forms thereof, which will entail special treatment guidelines in each case. The main purpose of treatment is to eradicate the microorganism from the entire urinary tract, taking into account whether it is a simple or complicated UTI in which the urinary emptying mechanism is affected or there are foreign bodies.

Antimicrobial treatment is administered under the following recommendations:

- Oral route is recommended.
- Bactericidal antibiotics are preferred over bacteriostatic agents.
- They should not be associated with each other, since a microorganism in bacteriostasis is less sensitive to a bactericidal agent.
- The antimicrobials with the highest urinary elimination in active state are chosen, considering the pH.
- Those with a limited spectrum of action are preferably used to modify the patient's flora as least as possible. In case of reinfection, it will be changed for another until the orientation of the antibiogram is known.[34]
- Caution will be taken with nephrotoxic antibiotics, adjusting the dose according to creatinine clearance or, if not available, to the estimated glomerular filtration rate.
- Those antimicrobial agents for which local resistance is greater than 20% in the case of cystitis and greater than 10% in the case of pyelonephritis should be avoided in empirical treatment.[34]
- Peritoneal dialysis and hemodialysis are capable of filtering out different antimicrobials, which should be avoided, adjusted or administered after dialysis[35] (Table 3).

There is no evidence in the medical literature that antimicrobial treatment can prevent the complications of a serious UTI. The poor correlation between the severity of the symptoms and the risk of permanent kidney damage, which is very small in terms of the

Table 3. Antimicrobials dialyzed in peritoneal dialysis and hemodialysis

Antimicrobial		
Dialyzed	**Dialyzed**	**Dialyzed**
Aminoglycosides	Cotrimoxazole	Amphotericin B
Amoxicillin	Erythromycin Fluoroquinolones	Ethambutol
Ampicillin	Vancomycin	Isoniazid
Aztreonam		Methycillin
Carbenicillin		Rifampicin
Cephalosporins		Teicoplanin
Fluconazole		
Metronidazole		

progression of the CKD, leads to not exceeding the prescription of antibiotics beyond the necessary to suppress the acute inflammatory reaction.[36]

Urine pH and osmolality can influence the antibacterial efficacy, especially in the case of aminoglycosides.[37] All penicillins reach high concentrations in urine, but ciprofloxacin has levels higher than amoxicillin with clavulanic acid.[38] The same occurs with levofloxacin, but not with other quinolones such as gemifloxacin and moxifloxacin, which have low urinary concentrations. Nitrofurantoin is not indicated in patients with creatinine clearance lower than 40 ml/min due to little or no excretion in urine.[39]

Antimicrobial treatment of **complicated UTI** (it is by definition in patients with CKD) will be carried out with a single dose of 3 g of fosfomycin, or treatment with nitrofurantoin for seven days (provided that the GFR is higher than 40 ml/min).[31] Other alternatives are seven days with amoxicillin-clavulanate or a fluoroquinolone (only if local resistance is low for these agents) in case of allergy to beta-lactam antibiotics.[40] In pyelonephritis, the choice of the antibiotic is conditioned by the special need for penetration into the renal parenchyma and the duration is 10-14 days, parenterally at the beginning if the patient meets the admission criteria. Quinolones are more effective in penetrating the parenchyma, but they do not show activity against enterococci, so they are not recommended in our environment.

In patients with CKD and **community-acquired pyelonephritis** without specific risk factors for colonization by multidrug-resistant enterobacteria, empirical treatment with cefuroxime or a third-generation cephalosporin is recommended, which will be replaced in case of allergy by fosfomycin, or as a last resort by aztreonam or an aminoglycoside (taking special care due to its nephrotoxicity). In the case of risk factors for the presence of multiresistant microorganisms (diabetes *mellitus*, indwelling urinary catheter, hemodialysis), ertapenem is recommended, although other carbapenems or piperacillin-tazobactam are accepted alternatives. In case of allergy to penicillin, the alternative is the use of intravenous fosfomycin sodium, resorting to amikacin as the last option under close monitoring of renal function due to its nephrotoxicity. (In the case of a patient already on dialysis, nephrotoxicity will not constitute a limitation for its use at the doses that correspond to this condition).[31]

In the case of **healthcare-associated pyelonephritis**, the first choice is a carbapenem with anti-pseudomonal activity, or piperacillin-tazobactam. In allergic patients, aztreonam, intravenous fosfomycin sodium, amikacin should be considered as a last

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resort, or the combination of the latter two agents (Table 4). It is recommended to associate coverage for enterococcus in patients with nosocomial pyelonephritis and severe sepsis or risk of endocarditis (e.g., for being a heart valve bearer). As soon as the antibiogram is available, antibiotic therapy should be adjusted reducing coverage. If in the next 48-72 hours the patient with pyelonephritis is afebrile and stable, is switched to oral treatment according to the antibiogram and is maintained for 10-14 days. The persistence of fever at 72 hours of treatment or worsening during treatment may be due to acute focal bacterial nephritis, focal suppurative complication, urinary obstruction, papillary necrosis, emphysematous pyelonephritis and an antibiotic resistant microorganism.[41] UTI caused by yeasts in diabetic patients or with indwelling catheters, even asymptomatic, should be treated with antifungal agents (fluconazole, voriconazole, amphotericin B); removal of the catheter is usually necessary to eliminate the source of infection.

Once the treatment is finished and after 48 hours, it is advisable to perform a control culture to detect recurrent infections due to therapeutic failure. Subsequent infections should be considered for long-term treatment (reinfections) or the study of possible pyelonephritic lesions or urological pathology (relapses).[41,42]

In the case of multiresistant microorganisms, the use of fosfomycin has proven to be useful in blocking the first step of the synthesis of the bacterial wall of a variety of both Gram-positive and Gram-negative microorganisms, and exerting synergy with other antimicrobials.[43]

Vaccination in UTI

Vaccines for recurrent UTI are intended to reduce the frequent use of antibiotics, adverse events, and bacterial resistance, prolonging the interval

Table 4. Guidelines for the treatment of UTIs in CKD.

Urinary tract infection (complicated by definition in CKD)	
Usual treatment for 7 days (except with fosfomycin): Fosfomycin-trometamol 3 g in a single dose Nitrofurantoin (Only if eGFR > 40 ml / min) Amoxicillin clavulanate 500/125 mg every 8 h Ciprofloxacin 250-500 mg/12 h (only if low local resistances) Levofloxacin 500 mg/24 h (only if low local resistances)	
Acute pyelonephritis Treatment 10 to 14 days. Intravenous route if there are criteria for admission. Adjust dose to renal function.	
No risk factors for multidrug resistance	
No allergy to beta-lactams	Allergy to beta-lactams
Cefuroxime 3rd generation cephalosporin	Fosfomycin Aztreonam Aminoglycosides (last option)
With risk factors for multidrug resistance	
No allergy to beta-lactams	Allergy to beta-lactams
Ertapenem Piperacillin-tazobactam	Aztreonam IV Fosfomycin sodium ± amikacin (last option)

between infections or radically reducing their incidence.

In a meta-analysis conducted by Naber *et al*.[44] with the vaginal vaccine SolcoUrovac® and the oral Uro-Vaxom®, it was observed that the number of UTIs was significantly lower in the patients treated with the oral vaccine. The vaginal vaccine was effective when it was administered with a booster cycle (50% of non-recurrence versus 14% with placebo).

The individualized bacterial vaccine Uromune®, which is applied sublingually for a minimum of three months and acts as an immunomodulator for the prevention of recurrent UTI, has been available since 2010. It contains whole bodies of selected inactivated bacteria from the main organisms that cause these infections: *E. coli, Proteus vulgaris, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus saprophyticus* and *Proteus mirabilis*.[45]

Lorenzo-Gómez *et al*.[46] retrospectively studied 669 women with recurrent UTI: 339 had taken antibiotic prophylaxis for six months and 360 had received the Uromune® sublingual bacterial vaccine for three months. All patients (100%) treated with antibiotics had at least one episode of UTI during the 12-month follow-up period, with a mean of 19 days free of UTI and a range of 5-300 days, while only 35 patients (9.7%) of the Uromune® group presented it. The reduction of the absolute risk amounted to 90.28% and the number of patients needed to treat was 1.1. The same authors[47] compared Uromune® for 3 months versus prophylaxis with trimethoprim sulfamethoxazole (200/40 mg/day) in 319 women. The 159 patients who received Uromune® experienced a significant reduction in the number of UTIs compared to the 160 who received the antibiotic (0.36 vs. 1.6, respectively, p <0.0001). A significant reduction was also observed at 9 and 15 months (p <0.0001). The number of patients who did not have any UTI at 3, 9 and 15 months were 101, 90 and 55 in the Uromune® group and 9, 4 and 0 in the antibiotic prophylaxis group.

Yang B *et al*.[48] treated with Uromune® for three months 77 women with recurrent UTI, of whom 75 completed the treatment, and they found that 78% of them did not have any UTI episode during the follow-up period, which lasted 12 months.

There are no published studies on the use of the bacterial vaccine in the population with UTI and CKD. In a series of more than 50 patients with recurrent UTI and CKD, treated with the bacterial vaccine in our center, the Hospital La Mancha-Centro de Alcázar de San Juan (Ciudad Real, Spain), It was observed that, after two years, one fifth of the subjects have not had a UTI again and the number of episodes was reduced by two thirds.

However, the results of clinical trials have shown limited efficacy, but they are too few to draw conclusions.[49] More studies are needed in the population with CKD to assess the benefits of sublingual vaccination to prevent UTI and the efficacy of extending the duration of vaccination to six months, due to predisposing and concomitant factors for the appearance of UTI and the decreased response to other vaccines in these patients.[50]

Other treatments for UTI

The fruit and the leaves of the red cranberry (*Vaccinium macrocarpon*) have been used for the prevention of UTI (cystitis and urethritis) due to their antioxidant effect. Due to bacterial resistances and the frequency of recurrent UTI, there is a growing interest in its use, but the studies carried out do not show sufficient evidence due to the high rate of treatment abandonment because of its low long-term acceptability.[37-39]

Conclusions

The population with CKD has a high prevalence of risk factors for UTI, which appears more frequently the more advanced the stage of kidney disease, which in turn contributes to its progression. When establishing the treatment, the need to adjust the dose of antibiotics to glomerular filtration, the use of non-nephrotoxic alternatives and the higher frequency of enterobacteria and multiresistant microorganisms in this population group must be

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taken into account. Specific studies are required to verify the efficacy and safety of alternative treatments and vaccines that minimize the use of antibiotic therapy and thereby, the problem of multidrug resistance in this type of patients.

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Conflict of interest

The authors declare no conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that patient data do not appear in this article.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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References

1. Ll. A. Localización de las infecciones. Prevalencia de las infec- ciones en los hospitales españoles. Estudio EPINE. Resultados de los estudios de 2004, 2005, 2006 y 2007 y evolución 1990-2007: 18 años. Medicina Preventiva 2008;14:22-6.
2. KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney international 2012;(Suppl) 2013(3 (1)):1-308.
3. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney international 2000;58(4):1758-64. Available from: https://doi.org/10.1111/j.1523-1755.2000. 00337.x
4. Naqvi SB, Collins AJ. Infectious complications in chronic kidney disease. Adv Chronic Kidney Dis 2006;13(3):199-204. Available from: https://doi.org/ 0.1053/j.ackd.2006.04.004
5. Dalrymple LS, Katz R, Kestenbaum B, de Boer IH, Fried L, Sarnak MJ, et al. The risk of infection-related hospitalization with decreased kidney function. Am J Kidney Dis. 2012;59(3):356-63. Available from: https://doi.org/10.1053/j.ajkd.2011.07.012
6. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al. CKD and risk of hospitalization and death with pneumonia. American journal of kidney diseases: the official journal of the National Kidney Foundation 2009;54(1):24-32. Available from: https://doi.org/10.1053/j.ajkd.2009.04.005
7. McDonald HI, Thomas SL, Nitsch D. Chronic kidney disease as a risk factor for acute community-acquired infections in high-income countries: a systematic review. BMJ Open2014;4(4):e004100. Available from: https://doi.org/10.1136/bmjopen-2013-004100
8. Cheikh Hassan HI, Tang M, Djurdjev O, Langsford D, Sood MM, Levin A. Infection in advanced chronic kidney disease leads to increased risk of cardiovascular events, end-stage kidney disease and mortality. Kidney Int 2016;90(4):897-904. Available from: https://doi.org/10.1016/j.kint.2016.07.013
9. Ching C, Schwartz L, Spencer JD, Becknell B. Innate immunity and urinary tract infection. Pediatr Nephrol. 2019 Jun 13. Availa- ble from: https://doi.org/10.1007/s00467-019-04269-9.
10. Kara E, Sakaci T, Ahbap E, Sahutoglu T, Koc Y, Basturk T, et al. Posttransplant Urinary Tract Infection Rates and Graft Outcome in Kidney Transplantation for End-Stage Renal Disease Due to Reflux Nephropathy Versus Chronic Glomeru- lonephritis. Transplant Proc. 2016 Jul-Aug; 48(6):2065-71.
11. Ito K, Goto N, Futamura K, Okada M, Yamamoto T, Tsujita M, et al. Death and kidney allograft dysfunction after bacteremia. Clin Exp Nephrol 2016;20(2):309-15. Available from: https://doi.org/10.1007/s10157-015-1155-6
12. Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. BMC Pregnancy Childbirth 2016;16(1):336. Available from: https://doi.org/10.1186/s12884-016-1128-0
13. Lee JR, Bang H, Dadhania D, Hartono C, Aull MJ, Satlin M, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. Transplantation 2013;96(8):732-8. Available from: https://doi.org/10.1097/ TP.0b013e3182a04997
14. Nicolle LE. Urinary tract infection in diabetes. Curr Opin Infect Dis 2005;18(1):49-53. Available from: https://doi.org/10.1097/00001432-200502000-00009
15. Geerlings SE, Stolk RP, Camps MJ, Netten PM, Hoekstra JB, Bouter KP, et al. Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group. Dia- betes Care 2000;23(6):744-9. Available from: https://doi.org/10.2337/diacare.23.6.744
16. Dalet F BE, De Cueto M, Santos M, De la Rosa M. La infección urinaria. Recomendaciones de la Sociedad Española de Enfer- medades Infecciosas y Microbiología Clínica. Procedimientos en Microbiologia Clínica 2003;14.
17. Andreu Domingo A CJ, Coira Nieto A, Lepe Jiménez JA. Diag- nóstico microbiológico de las infecciones del tracto urinario. Recomendaciones de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Procedimientos en Microbiología Clínica 2010;14.

18. Neumann I, Moore P. Pyelonephritis (acute) in non-pregnant women. BMJ Clin Evid 2014;2014.

19. Gordon I, Barkovics M, Pindoria S, Cole TJ, Woolf AS. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. J Am Soc Nephrol 2003;14(3):739-44. Available from: https://doi.org/10.1097/01.asn.0000053416.93518.63

20. Informe de diálisis y trasplante de 2015. XLVI Congreso Na- cional de la Sociedad Española de Nefrología; Oviedo 2016.

21. Pigrau C. [Nocosomial urinary tract infections]. Enferm Infecc Microbiol Clin 2013;31(9):614-24. Available from: https://doi.org/10.1016/j.eimc.2012.11.015

22. Ho HJ, Tan MX, Chen MI, Tan TY, Koo SH, Koong AYL, et al. Interaction between Antibiotic Resistance, Resistance Genes and Treatment Response for Urinary Tract Infections in Primary Care. J Clin Microbiol. 2019 Jun 26. pii: JCM.00143-19. Available from: https://doi.org/10.1128/JCM.00143-19

23. Hooton TM. The current management strategies for community-acquired urinary tract infection. Infect Dis Clin North Am 2003;17(2):303-32. Available from: https://doi.org/10.1016/s0891-5520(03)00004-7

24. Roberts JA. Management of pyelonephritis and upper urinary tract infections. Urol Clin North Am 1999;26(4):753-63. Available from: https://doi.org/10.1016/s0094-0143(05)70216-0

25. Bouza E, San Juan R, Munoz P, Voss A, Kluytmans J, Co- operative Group of the European Study Group on Nosocomial I. A European perspective on nosocomial urinary tract infections II. Report on incidence, clinical characteristics and outcome (ESGNI-004 study). European Study Group on Nosocomial Infection. Clin Microbiol Infect 2001;7(10):532-42. Available from: https://doi.org/10.1046/j.1198-743x.2001.00324.x

26. Rishpana MS, Kabbin JS. Candiduria in Catheter Associated Urinary Tract Infection with Special Reference to Biofilm Production. J Clin Diagn Res 2015;9(10):DC11-3. Available from: https://doi.org/10.7860/JCDR/2015/13910.6690

27. Oteo J, Delgado-Iribarren A, Vega D, Bautista V, Rodriguez MC, Velasco M, et al. Emergence of imipenem resistance in clinical Escherichia coli during therapy. Int J Antimicrob Agents 2008;32(6):534-7. Available from: https://doi.org/10.1016/j.ijantimicag.2008.06.012

28. Mena A, Plasencia V, Garcia L, Hidalgo O, Ayestaran JI, Alberti S, et al. Characterization of a large outbreak by CTX-M-1-producing Klebsiella pneumoniae and mechanisms leading to in vivo carbapenem resistance development. J Clin Microbiol 2006;44(8):2831-7. Available from: https://doi.org/10.1128/ JCM.00418-06

29. Rodriguez-Bano J, Pascual A. Clinical significance of exten- ded-spectrum beta-lactamases. Expert Rev Anti Infect Ther 2008;6(5):671-83. Available from: https://doi.org/10.1586/14787210.6.5.671

30. Lopez-Cerero L, Almirante B. Epidemiology of infections caused by carbapenemase-producing Enterobacteriaceae: reservoirs and transmission mechanisms. Enferm Infecc Microbiol Clin 2014;32 Suppl 4:10-6. Available from: https://doi.org/10.1016/S0213-005X(14)70169-7

31. De Cueto M, Aliaga L, Alos JI, Canut A, Los-Arcos I, Martinez JA, et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm fecc Microbiol Clin 2016. Available from: https://doi.org/10.1016/j.eimc.2016.11.005

32. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis. 2004;38(8):1150-8. Available from: https://doi.org/10.1086/383029

33. Kass EH, Finland M. Asymptomatic infections of the urinary tract. J Urol 2002;168(2):420-4. Available from: https://doi.org/10.1097/00005392-200208000-00004

34. Linhares I, Raposo T, Rodrigues A, Almeida A. Frequency and antimicrobial resistance patterns of bacteria implicated in community urinary tract infections: a ten-year surveillance study (2000-2009). BMC Infect Dis 2013;13:19. Available from: https://doi.org/10.1186/1471-2334-13-19

35. Infectious Lamarche C, Iliuta IA, Kitzler T. Disease Risk in Dialysis Patients: A Transdisciplinary Approach. Can J Kidney Health Dis. 2019 Apr 29;6. Available from: https://doi.org/10.1177/2054358119839080

36. Chiu PF, Huang CH, Liou HH, Wu CL, Wang SC, Chang CC. Long-term renal outcomes of episodic urinary tract infection in diabetic patients. J Diabetes Complications 2013;27(1):41-3. Available from: https://doi.org/10.1016/j.jdiacomp.2012.08.005

37. Papapetropoulou M, Papavassiliou J, Legakis NJ. Effect of the pH and osmolality of urine on the antibacterial activity of gentamicin. J Antimicrob Chemother 1983;12(6):571-5. Available from: https://doi.org/10.1093/jac/12.6.571

38. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA 2005;293(8):949-55. Available from: https://doi.org/10.1001/jama.293.8.949

39. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. Ann Pharmacother. 2013;47(1):106-11. Available from: https://doi.org/10.1345/aph.1R352

40. Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncompli- cated pyelonephritis pyelonephritis in women: a randomized trial. JAMA. 2000;283(12):1583-90. Available from: https://doi.org/10.1001/jama.283.12.1583

41. Grabe M B-JT, Botto H, Wullt B, Çek M, Naber KG, et al. UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression. Guidelines on urological infections. Guidelines of the European Association of Urology Arnhem, The Netherlands. 2011:45-56. Available from: https://doi.org/10.1086/320900

42. Snydman DR. Posttransplant microbiological surveillance. Clin Infect Dis 2001;33 Suppl 1:S22-5. Available from: https://doi.org/10.1086/320900

43. Seroy JT, Grim SA, Reid GE, Wellington T, Clark NM. Treatment of MDR urinary tract infections with oral fosfomycin: a retrospective analysis. J Antimicrob Chemother 2016;71(9):2563-8. Available from: https://doi.org/10.1093/jac/dkw178

44. Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta- analysis. Int J Antimicrob Agents 2009;33(2):111-9. Available from: https://doi.org/10.1016/j.ijantimicag.2008.08.011

45. Benito-Villalvilla C, Cirauqui C, Diez-Rivero CM, Casanovas M, Subiza JL, Palomares O. MV140, a sublingual polyvalent bacterial preparation to treat recurrent urinary tract infections, licenses human dendritic cells for generating Th1, Th17, and IL-10 responses via Syk and MyD88.Mucosal Immunol 2017;10(4):924-35. Available from: https://doi.org/10.1038/mi.2016.112

46. Lorenzo-Gómez MF, Padilla-Fernández B, García-Cenador MB, Virseda-Rodríguez ÁJ, Martín-García I, Sánchez-Escudero A, et al. Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections. Front Cell Infect Microbiol 2015;5:50. Available from: https://doi.org/10.3389/fcimb.2015.00050

47. Lorenzo-Gomez MF, Padilla-Fernandez B, Garcia-Criado FJ, Miron-Canelo JA, Gil-Vicente A, Nieto-Huertos A, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics. Int Urogynecol J 2013;24(1):127-34. Available from: https://doi.org/10.1007/s00192-012-1853-5

48. Yang B, Foley S. First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®. BJU Int 2018; 121(2):289-292. Available from: https://doi.org/10.1111/bju.14067

49. Hopkins WJ, Elkahwaji J, Beierle LM, Leverson GE, Uehling DT. Vaginal mucosal vaccine for recurrent urinary tract infections in women: results of a phase 2 clinical trial. J Urol. 2007;177(4):1349-53; quiz 591. Available from: https://doi.org/10.1016/j.juro.2006.11.093

50. Asadi Karam MR, Habibi M, Bouzari S. Urinary tract infection: Pathogenicity, antibiotic resistance and development of effective vaccines against Uropathogenic Escherichia coli. Mol Immunol. 2019 Apr; 108:56-67. Available from: https://doi.org/10.1016/j.molimm.2019.02.007

http://dx.doi.org/10.22265/acnef.7.1.264