Original Paper

Urinary tract infection with *Klebsiella pneumoniae* in Patients with Chronic Kidney Disease

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ABSTRACT: Study Motivation: After assessing electronic databases of medical scientific literature, we have observed that the interrelation between urinary tract infections (UTIs) and chronic kidney disease (CKD) is poorly studied, especially when UTIs are caused by Klebsiella pneumoniae (K. pneumoniae). Materials and methods: K. pneumoniae was isolated in 14 urine samples from patients with CKD addmited in the Nephrology Department of the County Emergency Clinical Hospital Craiova. The isolated strains were statistically analyzed in the correlation with the different clinical and functional parameters (age, gender, CKD stage, comorbidities, biochemical parameters-serum urea, creatinine, uric acid and blood electrolytes). The degree of K. pneumoniae susceptibility to antibiotics from different pharmacodynamic classes was assessed. Results: UTIs with K. pneumoniae in patients with CKD in the investigated period represented 0.51% from the total admissions in the clinic and 32.60% from cases of UTI. Eleven patients with this type of infection (78.56%) were in stage 4 and 5 CKD, and from them 4 also had diabetes mellitus type 2 (28.57%). We observed an increased level for serum creatinine (100%), blood urea (85.71%), and serum uric acid (45.45%). Two patients died after installation of cardiovascular changes in CKD, at advanced ages and in the presence of urinary infection. Multiple drug resistance occurred in 6 strains of K. pneumoniae correlated with the degree of kidney failure, advanced age, male gender, and diabetes mellitus. Conclusions: UTI with K. pneumoniae in patients with CKD is the second cause of urinary infection which raises problems of unfavorable evolution of CKD and also the recurrence of UTI with multiple drug resistance in CKD, which may lead to pharmacotherapeutical problems.

KEYWORDS: *Klebsiella pneumoniae, urinary tract infection (UTI), chronic kidney disease (CKD), antibiotics, susceptibility, multiresistance*

Introduction

Klebsiella pneumonia is the most relevant human pathogen within genus *Klebsiella*, causing many infections in hospitals, long-term care facilities and communities worldwide, including lung, urinary tract, abdominal cavity, surgical sites and soft tissues infections, even bacteremia [1,2]. This capsulated Gram-negative bacterium is found in normal flora of the mouth, skin and intestine, and it is also the third most frequently isolated microorganism in the blood cultures from sepsis patients [3]. A new hypervirulent (hypermucoviscous) variant of *K. pneumoniae*, determining severe and life-threatening infections, including pyogenic liver abscesses, endophthalmitis and meningitis, has been described and is becoming a public health concern [2,4,5].

It is important to underline that *Klebsiella pneumoniae* is one of the most common pathogens in nosocomial infections, and tends to become multidrug-resistant [3]. The hospitalized, immunocompromised patients with significant underlying diseases are the main targets of this pathogenic bacteria [1]. The underlying molecular mechanisms involved in the pathogenesis of infections with this microorganism are not entirely elucidated. Endocytosis regulating protein caveolin-1 is implicated in inflammatory responses in *K. pneumoniae* infection. The Src tyrosine kinase Lyn, involved in monocyte-related phagocytosis through FcγR via the phosphorylation of tyrosines in immunoreceptor tyrosine-based activation motifs, may coordinate lipid rafts and impact cellular function of caveolin-1. Lyn is located in the proximity of lipid rafts and can be translocated into the activated membrane domains to transmit cellular signals, thus being involved in host defense against *K. pneumoniae* by regulating the phagocytosis processes and downregulating inflammatory responses [3,6]. Lyn deficiency could accelerate and intensify cytokine responses (such as cytokines IL-6, tumor necrosis factor TNF-*alpha*) in mice infected by *K. pneumoniae*. Lyn cooperating with lipid rafts regulates inflammatory responses in *K. pneumoniae* infection through the p38/NF-κB pathway [3].

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem [7]. Patients with CKD and kidney failure may be at hight-risk for infectious complications, similar to patients with other tipes of acquired immune deficiencies or those treated with immunosuppresive drugs. Secundary immune alterations in uremia are multifaceted and influenced by uraemic intoxication *per se*, by altered renal metabolism of immunologically active proteins and by specific effects of therapy [8]. Dialysis causes additional immune abnormalities [8]. End-stage renal disease (ESRD) is associated with significantly increased morbidity and mortality resulting from cardiovascular disease (CVD) and infections, accounting for about 50% and 20%, respectively, of the total mortality in ESRD patients [9]. It is plausible that these complications are linked to alterations in the immune system functions in ESRD. Uremia is associated with immune dysfunctions characterized by an impaired immune response component that contributes to the high prevalence of infections among these patients, as well as by a persistent immune stimulation component resulting in inflammation that may contribute to CVD [9,10]. Accelerated atherosclerosis in ESRD may involve interrelated processes, including oxidative stress, endothelial dysfunction and vascular calcification, in a milieu of constant low-grade inflammation with impaired function of T cells and neutrophils, as well as a dysregulated cytokine network, the mainly proinflammatory cytokines IL-6 and TNF-*alpha* playing key roles in the development of Th imbalance and CVD [11]. Chronic renal failure is a risk factor for the development of urinary tract infections (UTIs) due to metabolic disorders resulting in secondary immune alterations affecting many components of the immunity. Moreover, in patients with chronic renal failure, UTIs occur frequently after kidney transplantation [12].

We found few studies related to the relationship between UTIs and CKD, by assessing electronic databases of medical scientific literature, and fewer studies of uropathogenic *K. pneumoniae* resistance to antibiotics in these cases. The management of UTIs in patients with chronic renal failure has drawn little attention [13].

We investigated the interrelation between *Klebsiella pneumoniae* UTIs and CKD, by evaluating clinical and laboratory correlations. We also assessed antibiotic susceptibility of the uropathogen. An important aim of the study is to highlight whether CKD and chronic renal failure can be associated with antibiotic resistance of *K. pneumoniae* isolates in the UTIs.

The **objectives** are to determine the frequency of UTIs with *Klebsiella pneumoniae* in CKD, assessing clinical forms of the chronic kidney disease, favorable factors, co-morbidities and the influence of the infection on the evolution of chronic kidney failure and the degree of antibiotic susceptibility of uropathogenic *K. pneumoniae.*

Study design

The clinical study was conducted at the Nephrology Department and the hospital's Bacteriology Laboratory of the County Emergency Clinical Hospital Craiova for the period July 1-December 31, 2016.

Laboratory screening of CKD was performed by determining serum creatinine, urea, uric acid and proteinuria.

CKD is defined as “Either kidney damage or GFR of less than 60mL/min/1.73m2 of body surface area lasting for long than 3 months” [14].

We determined the stages of CKD based on the GFR (Glomerular Filtration Rate) estimate which is calculated from serum creatinine according to the KDOQI guidelines (National Kidney Foundation's Kidney Disease Outcomes Quality Initiative):

Stage 1: GRF $\geq$ 90mL/min/1.73m^2

Stage 2: GRF = 60-89mL/min/1.73m^2

Stage 3: GRF = 30-59mL/min/1.73m^2

Stage 4: GRF = 15-29mL/min/1.73m^2

Stage 5: GRF < 15 mL/min/1.73m^{2}or dialysis

Normal age-related decline in GFR is ~1mL/min/1.73m^2/yr after 30–40 years of age.

We evaluated the risk factors (diabetes mellitus, urolithiasis, hydronephrosis etc).

To evaluate correlations between UTIs, CKD and antibiotic resistance of *K. pneumoniae,* we assessed:

- demographic parameters of the study group: age, gender, the environment of origin (urban, rural);
- CKD stage by determining serum creatinine, urea, uric acid, GFR;
- blood electrolytes determination (serum sodium, potassium);
- state of performing or not hemodialysis;
- ultrasound examination with detection of anatomical anomalies of the kidneys and the presence of kidney stones;

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- patient history such as diabetes, hypertension, recurrent UTIs, nephrolithiasis, glomerulonephritis, pyelonephritis.

Exclusion criteria were represented by renal transplantation, renal tuberculosis, lupus nephritis, pregnancy, personal history of recent urogenital instrumentation, hypersensitivity /allergy to the tested antibiotics.

Urine cultures for patients included in the study were carried out in the Department of Bacteriology of the hospital laboratory, and antibiotic susceptibility/resistance testing was determined by antibiogram after detection of the causative microorganism of UTIs *(Klebsiella pneumoniae*).

Antibiotic susceptibility

Antibiotic susceptibility of *K. pneumoniae* isolates was done by Bauer's and Kirby's disk diffusion method [15]. Organisms were grown on specific media and inoculated on Mueller Hinton agar plates by sterile swabs and then antibiotic disks were placed on media and pressed gently followed by overnight incubation. This method was done according to Clinical and Laboratory Standards Institute (CLSI) guidelines to determine susceptibility of UTIs causative agents [15].

We have complied with standardized procedures for antimicrobial susceptibility of the drugs tested presented in M02, M07 and M100 with the supplement in M100 S25 (January 2015) that include data essential to drug selection, quality interpretation and control required for clinical practice [16].

In this study the antibiotic disks used for antibiogram were:

Beta-lactams+beta-lactamase inhibitors: Amoxicillin+Clavulanic acid (AMC), Piperacillin+tazobactam (TPZ), Cefoperazone+sulbactam (CES);

Cephalosporins: Cefazoline (CZ) first generation, Cefuroxime (CXM), Cefoxitin (FOX) and Cefaclor (CEC), second generation, Ceftriaxone (CRO), Ceftibuten (CTB) and Cefpodoxim (CPO), third generation, Cefepime (FEP) fourth generation;

Carbapenems: Imipenem (IP);

Fluoroquinolones: Ciprofloxacin (CPR), Ofloxacin (OFX), Norfloxacin (NOR);

Aminoglycosides: Gentamicin (GN), Amikacin (AK);

Polymyxins: Colistin (CO);

Folate pathway inhibitors: Trimethoprim/ sulfamethoxazole (SXT);

Nitrofurans-Nitrofurantoin (FM);

Phosphonic acid derivate: Fosfomicin trometamol (FOT).

The study was retrospective, descriptive and non-randomized.

Data obtained from patients in 2016 were compared with similar data obtained previously in 2010, to assess changes.

Statistical analysis

The antibiotic resistance data was recorded in MS-Excel and the statistical analysis of the data was performed and statistical significance between different parameters was checked by Chi-square test, *t*-test and the Statistical Package for the Social Sciences (SPSS) 13.0 for Windows. A p value of ≤ 0.05 was considered significant. Differences between groups were tested by use of the x2 and Student's *t* test. Also were used the logistic regressions for elaboration of predictive model.

Results

Prevalence of *Klebsiella pneumoniae* uropathogens *in CKD*

In the Nephrology Department between July 1 and December 31, 2010, 357 patients were hospitalized, from which 37 (10.36%) had UTIs with 12 cases (32.43%) with CKD and *K. pneumoniae* UTI, from them 10 (27.03%) being male and 2 (5.40 %) female patients (Table 1,2).

In 2016, in the last 6 months, of the 272 admitted patients 46 (16.91%) had UTIs, from which 15 (32.60%) with *K. pneumoniae*, 8 (17.08%) men and 7 (15.22%) women (1 women without CKD) (30.43% patients had UTI with *Klebsiella* and CKD) (Table 1,2).

In both time periods the main etiology of UTIs was *Escherichia coli*.

In the last 6 months of 2010, the rate of UTIs with uropathogenic germs in CKD patients was 37 (10.36%). In the same period of the year 2016 the percentage was 16.91% (46 patients). Compared to all patients admitted to the clinic during this time, UTIs with *K. pneumoniae* in patients with CKD accounted for 0.33% in 2010 and 0.51% in 2016 (Table 2).

There is no correlation in the prevalence of UTIs cases in patients with CKD linked to the hot or cold season of the year. In 2010, there were several UTIs cases with *K. pneumoniae* in August, November, and in 2016 in August, September, November (Table 2).

Table 1. Distribution of patients without UTI during July-December 2010 and 2016

Without UTI patients	Month of patient without UTI hospital admission (n)						
	Total	**July**	**August**	**September**	**October**	**November**	**December**
Females without UTI 2010	151	20	17	25	30	27	32
Males without UTI 2010	169	27	26	32	26	27	31
Total without UTI 2010	**320**	**47**	**43**	**57**	**56**	**54**	**63**
Females without UTI 2016	118	17	14	26	14	31	16
Males without UTI 2016	108	21	13	18	16	32	8
Total without UTI 2016	**226**	**38**	**27**	**42**	**30**	**63**	**24**

Table 2. Distribution of patients with Klebsiella pneumonia UTI and UTIs (total) during July-December 2010 and 2016

Urine culture	Total (n)	Month of patient with UTI hospital admission (n)					
		July	**August**	**September**	**Octomber**	**November**	**December**
Urine culture Klebsiella 2010	F (2)	0	0	0	1	1	0
	M (10)	2	4	0	1	3	
Urine culture Klebsiella 2010 - total	**12**	**2**	**4**	**0**	**2**	**4**	**0**
Urine culture Klebsiella 2016	F (7)	0	2	3	1	0	1
	M (8)	2	2	3	1	0	0
Urine culture Klebsiella 2016 -total	**15**	**2**	**4**	**6**	**2**	**0**	**1**
Total uropathogenic germs 2010	37	6	9	7	6	8	1
Total uropathogenic germs 2016	46	7	8	13	5	8	5

In the 2016 evaluation, we observed that the age of patients it's between 50 and 82, with an average age of 69.8 (Table 3).

Analyzing UTIs with *K. pneumoniae* in patients admitted to the Nephrology Department, it was found that it prevails at the age above 55 years, similar in the two studied periods of time.

In 2016, from 15 cases of UTIs with *K. pneumoniae*, in 14 (93.33%) the infection occurred in the patients with CKD and in one (6.67%) patient without CKD hospitalized for urinary infection and kidney cyst with nephrolithiasis.

Among patients with CKD, 6 (42.86%) were on renal dialysis (3 males and 3 females).

Although in 2010 UTIs with *K. pneumoniae* and CKD predominated in males (83.33%), in 2016 the proportion of males and females is quite similar, with a slight predominance in males (6→42.86% women and 8→57.14% men).

In 2016 from the patients with CKD, 3 (21.42%) patients were in the stage 3 of kidney failure, 3 patients (21.42%) in stage 4 and 8 (57.14%) patients in stage 5.

From the 14 cases with CKD and UTI with *K. pneumoniae*, 7 (50%) had also type 2 diabetes, of which 4 (28.57%) were in stage 4 and 5 of CKD.

Table 3. Distribution of UTI and CKD patients according to age group

	Age Distribution							
Age groups (years)	**<=25**	**26 - 35**	**36 - 45**	**46 - 55**	**56 - 65**	**66 - 75**	**>75**	Min and max ages.
Number of patients with UTI 2016	1 (2.17%)	0 (0%)	1 (2.17%)	3 (6.52%)	15 (32.60%)	14 (30.44%)	12 (26.08%)	**(min. 21 ages) (max.83 ages)**
Number of patients with *Klebsiella* UTI 2016	0 (0%)	0 (0%)	0 (0%)	1 (7.14%) (50 ages)	3 (20.14%) +1 patient without CKD (7.14%)	4 (28.57%)	6 (42.85%)	**(min.50 ages) (max. 82 ages)**

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Of the 14 patients with CKD and UTI, nephropathy without case specification was found in 6 (42.85%) patients, nephrolithiasis in 4 (28.57%) patients, and renal cyst in one case (7.14%).

Regarding biochemical parameters related to kidney function, increased blood urea was performed in 12/14 (85.71%) patients, 5/11 (45.45%) patients with increased uric acid, elevated serum creatinine in 14/14 (100%) patients. Proteinuria was found in 5/10 (50%) of CKD patients.

Blood electrolytes determinations revealed a decrease in serum sodium below normal values in 9/14 (64.29%) patients with CKD, serum potassium increased in 6/14 (42.86%) patients and 1/14 (7.14%) with low serum potassium compared to normal.

Antibiotic susceptibility

Patients with CKD are possibly more likely to have a resistant strain.

Among the *Klebsiella* strains tested on eight cephalosporins, there is a high resistance in the first and second generation ones (10/14-71.43% cefazoline-resistant, 3/4-75% to cefuroxime, 7/14-50% to cefoxitin, but also to 5/14-35.71% intermediate sensitivity to cefoxitin, 8/13-61.54% resistance to ceftriaxone). From third generation a moderate sensitivity to ceftibuten was found where 4/7-57.14% strains were susceptible. Unfortunately, in the cefepime (fourth generation cephalosporin) of the 4 tested strains 2 (50%) were resistant and 2 (50%) sensitive intermediates. In carbapenems, imipenem remains a reserve antibiotic with a good sensitivity to *K. pneumoniae* (10/14-71.43% susceptibiliy strains) (Table 4).

The combinations of betalactams-beta-lactamase inhibitors demonstrated that the best susceptibility of *K. pneumoniae* was to cefoperazone-sulbactam (6/7-85.71% susceptible strains) and also piperacillin-tazobactam (7/14-50% susceptible strains) (Table 4).

In the group of CKD many fluoroquinolones still retain good susceptibility (9/14-64.29% susceptible and 5/14-35.71% resistant to ciprofloxacin, 3/3-100% susceptible to ofloxacin and less to norfloxacin-3/7-42.86% susceptible, 4/7-57.14% resistant) (Table 4).

High sensitivity to aminoglycosides may be explained by their reduced use in CKD due to nephrotoxicity (5/14-35.71% to gentamicin and 11/13-84.62% to amikacin). However, the resistance to gentamicin is still quite high (5/14-35.71%) (Table 4).

High sensitivity has also been encountered with colistin for injection, maybe due to reduced use in CKD (11/11-100.00%) (Table 4).

Resistance is increased to trimethoprim/sulfamethoxazole (13/14-92.86%) and to nitrofurantoin (13/14-92.86% and one strain with intermediate sensitivity) probably due to more widespread use (Table 4). *Klebsiella* spp. are only moderately inhibited by nitrofurantoin [17].

For fosfomycin trometamol, currently used in single-dose for cystitis, the study reveales a high resistance with 7/14 (50%) resistant strains, 2/14 (14.29%) strains with intermediate susceptibility and only 5/14 (35.71%) susceptible strains (Table 4).

Of the 15 antibiotics tested in the *K. pneumoniae* UTI without CKD it was revealed resistance to ofloxacin, ciprofloxacin, ceftriaxone, trimethoprim / sulfametoxazole and nitrofurantoin, and susceptibility to gentamicin, amikacin, tazobactam/piperacillin, ceftibuten, imipenem, colistin, intermediate sensitivity to cefoxitin, cefazoline, fosfomycin trometamol and cefoperazone/sulbactam.

Table 4. Susceptibility patterns for Klebsiella pneumoniae isolated from urine samples of CKD patients (N-number, %)

Classes of antibiotics	Antibiotic used	Codes	Disks (μg)	Isolates (N)	Resistant N (%)	Intermediate N (%)	Susceptible N (%)
Beta-lactams							
Beta-lactam + beta-lacatamase inhibitors	**Amoxicillin+ Clavulanic acid**	AMC	20/10	4	3 (75)	0 (0)	1 (25)
	Piperacillin+ Tazobactam	TPZ	100/10	14	4 (28.57)	3 (21.43)	7 (50)
	Cefoperazone +sulbactam	CES	75/30	7	0 (0)	1 (14.29)	6 (85,71)
Cephalosporins	**Cefazolin 1rd generation**	CZ	30	14	10 (71.4)	3 (21.43)	1 (7,14)
	Cefuroxime 2rd generation	CXM	30	4	3 (75)	1 (25)	0 (0)
	Cefoxitin 2rd generation	FOX	30	14	7 (50)	5 (35,71)	2 (14.29)

	Cefaclor 2rd generation	CEC	30	1	1 (100)	0 (0)	0 (0)
	Ceftriaxone 3rd generation	CRO	30	13	8 (61.54)	2 (19.23)	2 (19.23)
	Ceftibuten 3rd generation	CTB	30	7	2 (28.57)	1 (14.29)	4 (57.14)
	Cefpodoxim 3rd generation	CPO	30	1	1 (100)	0 (0)	0 (0)
	Cefepime 4rd generation	FEP	30	4	2 (50)	2 (50)	0 (0)
Carbapenems	**Imipenem**	IP	10	14	3 (21.43)	1 (7,14)	10 (71.43)
Non-betalctams							
Quinolones	**Ciprofloxacin**	CPR	5	14	5(35.71)	0 (0)	9 (64.29)
	Ofloxacin	OFX	5	3	0(0)	0 (0)	3 (100)
	Norfloxacin	NOR	10	7	4(57.14)	0 (0)	3 (42.86)
Aminoglycozides	**Gentamicin**	GN	10	14	5(35.71)	4 (28.58)	5 (35.71)
	Amikacin	AK	3010	13	1(7.69)	1 (7.69)	11 (84.6)
Polymyxins	**Colistin**	CO		11	0(0)	0 (0)	11 (100)
Folate pathway inhibitors	**Trimethoprim/Sulfamethoxazole**	SXT/ TS	1.25/23 .75	14	13 (92.86)	0 (0)	1 (7.14)
Phosphonic acid derivatide	**Fosfomycin trometamol**	FOT	50	14	7(50)	2 (14.29)	5 (35.71)
Nitrofurans	**Nitrofurantoin**	FM	300	14	13 (92.86)	1 (7.14)	0 (0)

From all strains isolated of *K. pneumoniae*, over 70% were resistant to trimethoprim/ sulfamethoxazole (92.86%), nitrofurantoin (92.86%), cefazoline, cefalosporin of first generation (71.43%), and 75% strains were resistant to cefuroxime (second generation cephalosporin) and to amoxicillin/ clavulanic acid.

Table 5. Strains of multidrug resistant Klebsiella pneumoniae from patients with UTI and CKD

Klebsiella strains resistant to Ciprofloxacin + resistant to other antibiotics (n.)	*Klebsiella* resistant to other antibiotics	No. antibiotics tested	CKD stage	Hemo dialysis	Diabetes	Renal affecting	Age	Gender distribution
+7 antibiotics	FOX/CZ/TPZ/CTB/FM/ NOR/TS	14	4	0	+	L, C	66	M
+10	GM/FOX/CZ/TPZ/CTB/ FM/NOR/CRO/FEP/TS	14	5	+	+	0	79	M
+11	GM/FOX/CZ/FOT/TPZ/ FM/NOR/ CRO/IP/TS/CXM	15	3	0	+	L	50	M
+9	GM/CZ/FOT/FM/NOR/ CRO/TS/CXM/AMC	16	4	0	+	0	76	M
+8	GM/FOX/AK/CZ/TPZ/C RO/IP/TS	12	5	+	0	N	60	M
+5	***FM/CPR/CRO/OFX/TS***	***15***	***Without CKD***	***0***	***0***	***L, C***	***60***	***F***

L=lithiasis; C=renal cyst; N=nephropaty; M=male; F= female; n=number

Of the six ciprofloxacin resistant strains, five were multiresistant (for 12,11,10,9,8 antibiotics), and one strain from a CKD-free patient is resistant to 5 antibiotics from different pharmacodynamic classes (cephalosporins/ nitrofurans/ fluoroquinolones/ folate pathway inhibitors) (Table 5).

Although strain number 10 is sensitive to ciprofloxacin, it is resistant to other 8 antibiotics from 5 different pharmacodynamic classes (Table 6). It was isolated from a female patient aged 77 years with CKD stage 3 and diabetes.

By analyzing the sensitivity of the six strains, we found that they are resistant to more than four classes of antibiotics, which makes them fit into the group of *Klebsiella pneumoniae* multiresistant strains. The presence of multidrug resistant strains in advanced kidney disease (stage 4 and 5) is noted. Of the six patients with CKD, only two were on hemodialysis (Table 5).

Regarding the age of the patients with *K. pneumoniae* UTIs, three subjects were between 50 and 60 year-old (of which, one in CKD stage 3, one in stage 5, and one without CKD), and three patients were over 65 years (with stages 4 and 5 CKD) (Table 5).

Considering gender and CKD, five patients were men and only one woman. Four patients were from urban environment and two from rural environment (Table 4).

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Table 6. The resistance of Klebsiella pneumoniae strains to antibiotics and the number of classes of antibiotics

Klebsiella strains	Antibiotic resistance	Number of antibiotics	Number of classes of antibiotics
1	FOX/CZ/TPZ/CTB/FM/CPR/NOR/TS	8	5 classes
2	GM/FOX/CZ/TPZ/CTB/FM/CPR/NOR/CRO/FEP/TS	11	6 classes
3	GM/CZ/CRO/FEP/TS	5	4 classes
4	FOT/FM/TS	3	3 classes
5.	CZ/FM/CRO/TS	4	3 classes
6	FM/TS	2	2 classes
7	FOT/FM/TS	3	3 classes
8	GM/FOX/CZ/FOT/TPZ/FM/CPR/NOR/CRO/IP/TS/CXM	12	9 classes
9	FM/TS/AMC	3	3 classes
10	FOX/CZ/FOT/FM/CRO/TS/CXM/AMC	8	5 classes
11	GM/CZ/FOT/FM/CPR/NOR/CRO/TS/CXM/AMC	10	4 classes
12	FOX/CZ/FOT/FM/CRO/TS	6	6 classes
13	GM/FOX/AK/TPZ/FM/CPR/CRO/IP/TS	9	8 classes
14	FOX/CZ/FOT/FM/IP/CEC/CPO	7	4 classes
15 *	***FM/CPR/CRO/OFX/TS***	***5***	***4 classes***

*Klebsiella pneumoniae of patient without CKD

K. pneumoniae strains were defined as resistant multidrug strains following analysis of resistance and susceptibility to antibiotics tested for each strain. Using the median, standard deviation and variation coefficient, limits have been set for regrouping cases as having limited or extended multidrug resistance. Thus, subjects with strains resistant to less than 8 antibiotics were included in the first group, and if they had strains resistant to more than 8 antibiotics were considered with severe multidrug resistance.

Table 7. Observing-predicted frequency table for the two groups (limited and extended resistance), and risk factors

PROTEINURIA	CREATININE	UREA	URIC ACID	DIABETES	HEMODIALYSIS	CKD STAGE	URBAN/RURAL	AGE	GENDER	Multi Resistance	Frequency			Percentage	
											Observed	Predicted	Pearson Residual	Observed	Predicted
0	0	1	0	0	0	0	R	60	F	EXTENDED	0	,000	,000	,0%	,0%
										LIMITED	1	1,000	,000	100,0%	100,0%
	1	0	0	0	0	3	R	69	F	EXTENDED	0	,000	,000	,0%	,0%
										LIMITED	1	1,000	,000	100,0%	100,0%
		1	0	1	1	5	R	65	M	EXTENDED	0	,000	,000	,0%	,0%
										LIMITED	1	1,000	,000	100,0%	100,0%
			1	1	0	3	U	75	F	EXTENDED	1	1,000	,000	100,0%	100,0%
										LIMITED	0	,000	,000	,0%	,0%
1	1	1	0	1	1	5	U	79	M	EXTENDED	1	1,000	,000	100,0%	100,0%
										LMITED	0	,000	,000	,0%	,0%
			1	1	0	3	U	50	M	EXTENDED	1	1,000	,000	100,0%	100,0%
										LIMITED	0	,000	,000	,0%	,0%
						4	U	66	M	EXTENDED	1	1,000	,000	100,0%	100,0%
										LIMITED	0	,000	,000	,0%	,0%
								76	M	EXTENDED	1	1,000	,000	100,0%	100,0%
										LIMITED	0	,000	,000	,0%	,0%

From the multivariate analysis we can see that the common, defining elements of the multi-resistance group are: CKD stage 3-5, male gender, age over 70 years, urban environment, diabetes association, high levels of creatinine, urea and ureic acid, proteinuria. (Table 7). Each strain of *K. pneumoniae* is multidrug resistant to 8 and more than 8 antibiotics (Tables 5,6). The model used is predictive for 62.5% of investigated cases.

The frequency of resistance for each antibiotic from the extended multidrug resistance group and the limited drug resistant group was compared to determine which antibiotic should be avoided in patients with multidrug resistance.

Thus, in Gentamicin there are 66.4% cases of resistance in the extended multidrug resistance group, vs. 11% resistance in the limited resistance group (p=0.037); FOX 83% vs. 22.2% (p=0.007); CZ 100% vs. 44.4% (p=0.0003); TPZ

66.4% vs. 0% (p=0.025); CTB 100% vs. 0% (p <0.001); FM 100% vs. 88.8% (p=0.0006); CPR 83% vs. 11.1% (p=0.004); NOR 80% vs. 0% (p=0.01); TS 100% vs. 88% (p=0.0006); CXM 100% vs. 0% (p <0.001).

A similar sensitivity in both groups (p> 0.05) was found for: AK; FOT; IP; CES; CO. These antibiotics may be used in patients with UTI and CKD.

Noteworthy, a 77 year-old women with CKD stage 5 with nephropathy, hemodialysis, hypertension, heart failure and with *K. pneumoniae* UTI was hospitalized twice at interval of one month during the study period, and the *Klebsiella* susceptibility changed as follows. At the first admission, the *K. pneumoniae* revealed resistance to 3/16 tested antibiotics (nitrofurantoin, trimethoprim/ sulfamethoxazole, amoxicillin / clavulanic acid), intermediate sensitivity to 6/16 antibiotics and susceptibility to 7/16 antibiotics tested. At one month interval, at the second admission *Klebsiella pneumoniae* had resistance to 6/12 antibiotics, intermediate sensitivity to 1/12 antibiotics and susceptibility to 5/12 antibiotics. No susceptibility to norfloxacin, cefoperazone/ sulbactam, cefuroxime, amoxicillin/ clavulanic acid has been tested, which would possibly have shown *Klebsiella* resistance to these antibiotics. The patient died by cardiopulmonary arrest two weeks after the second hospitalization. In this patient, an increase in the resistance of urine isolated *K. pneumoniae* to the cephalosporins of first, second and third generation was observed. There was a change from intermediate susceptibility to resistance for three antibiotics (cefazoline, cefoxitin, ceftriaxone), and the sensitivity to imipenem decreased at intermediate sensitivity.

Another patient who died was an 82 year-old man with CKD stage 5, nephropathy, cardiac disease and UTI with *K. pneumoniae*. In his unfavorable evolution, it seems that cardiac damage prevailed, with death due to worsening of the renal failure and myocardial infarction. *K. pneumoniae* revealed resistance to three antibiotics (tazobactam/ piperacillin, fosfomycin tromethanol, trimethoprim/ sulfametazazole, from three different pharmacodynamic classes) and intermediate sensitivity to ceftriaxone and cefoxitin (another classes of antibiotics).

Discussions

In 2001, the European Commission presented a "Community strategy against Antimicrobial Resistance". An important part of this strategy is the „Council Recommendation on the prudent use of antimicrobial agents in human medicine". These proposals provide a detailed set of public health actions against antimicrobial resistance [18].

Urinary tract infections caused by *K. pneumoniae* appear to be increasing and have become a real health problem, especially in hospital settings. This trend should be approached even more carefully in patients with CKD, where urinary infection can accelerate evolution to the final stages of renal failure, infections being the second cause of mortality in these patients after cardiovascular complications.

Kidney disorders are increasing in prevalence, affecting mostly elderly people. Pharmacokinetics of kidney eliminated drugs is significantly altered, and drug dosage adjustments based on individual renal function must be performed [19].

CKD and other chronic illness, especially those which alter the immune system function, such as diabetes, may increase the risk of developing UTIs [20].

UTI involve the combination of pathogens within urinary tract and symptoms and/or inflammatory response to the pathogens requiring treatment. Asymptomatic bacteriuria is defined as isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen from an individual without clinical manifestations. UTIs are usually classified by the site of infection as cystitis or pyelonephritis [21].

The risk of developing chronic kidney insufficiency due to UTIs without other risk factors is low. The course and severity of UTIs are determined by the pathogenicity of the infective microorganism and the efficiency of local or systemic defense mechanisms. Virulence properties, given by adhesins, toxins or capsule, are encoded by the genomic structures. In kidney failure, many different molecules (uraemic toxins, betaine, amino acids, creatinine, urea, glucose) influence the microbial environment. Defense factors, such as phagocytic activity of granulocytes, defensins and Tamm-Horsfall protein, as well as the underlying anatomical lesions and the pre-existing renal disease determine the severity of UTIs and the prognosis of renal insufficiency [22]. In the presented study, we have seen a slightly decrease in percent, but with an increase in absolute number of UTI cases with *K. pneumoniae* after 6 years in patients with

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CKD (30.43% in 2016 as compared to 32.43% in 2010 versus 14 patients in 2016 and 12 patients in 2010). The age of patients with CKD and UTIs with *Klebsiella* admitted to the Nephrology Department shifted towards older age groups. This increase in the number of third-age CKD patients maybe due to the increase in the lifetime of the entire population, with improved medical care for renal patients.

In a study published by Taiwanese authors in patients with UTI and CKD with varying degrees of renal impairment, it was found that age, female gender, and kidney stones are independently associated with UTI in the upper urinary tract. This study revealed also that patients with CKD and UTI were elderly, and that females were prone to have more bacteriuria and upper UTI than males. In addition, subjects who had renal stones were more prone to have upper UTI than other bacteriuria patients [23]. In our study there is a higher proportion of elderly men with UTI and CKD.

UTIs prevalence is usually higher in women, at a younger age. *Klebsiella* infections are more prevalent in older groups [24]. Other authors mention a higher prevalence in women of the third age, but does not specify whether the patients had associated CKD [1,25]. A reduction in estimated glomerular filtration rate and/or the presence of proteinuria, are the predominant manifestations of CKD, which is common in the elderly population [26]. Proteinuria accelerates the rate of decline of GFR in hypertensive, diabetic, and non-diabetic individuals. Proteinuria was recorded in our study in 5/10 (50%) CKD patients (stage 3-one patient, stage 4-two patients and stage 5-two patients) aged 65-79 year-old. In 2014 some autors have stated that there is currently no evidence on the relationship between proteinuria and infection incidence independent of the glomerular filtration rate [27].

In another study, UTIs in dialyzed kidney patients were frequent, with *Klebsiella* as a second uropathogen involved [28]. In our study, from 14 patients with CKD, six underwent dialysis. Of these, a multiresistant *Klebsiella* was isolated in two patients.

While bacterial infections have diminished as a cause of death in the general population, they remain the second most common cause of death in patients ESRD. This is largely due to the impaired immune response in uremia which is caused by a decreased granulocyte and monocyte/macrophage phagocytic function, but also a defective antigen presenting capacity of antigen presenting cells and a depletion of the antigen presenting dendritic cells. Moreover, there is a reduction in number and antibody producing capacity of B cells, and an increased T cell turnover and apoptosis leading to depletion of naive and central memory CD4+and CD8+T cells, with an impaired cell mediated immunity [29]. In our study, the serum urea was above the normal range in 13/14 patients with CKD, contributing probable to decreased immunity, and favoring therefore *K. pneumoniae* UTI.

Predialysis kidney disease appears to be associated with increased risk of severe infection. Whether predialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear [30].

Complicated UTIs with relapsing *Klebsiella* infections are relatively more common in patients with diabetes [31]. Diabetes, as well as CKD, are risk factors for recurrent UTIs by decreasing immunity and therefore resistance to infection.

Diabetes represents the most common cause of chronic kidney disease. It is part of the first category of risk factors in the progression of CKD. Type 2 diabetes is not only a risk factor for community-acquired UTIs, but also for health care-associated UTIs, catheter-associated UTI and post-renal transplant-recurrent UTIs [32]. In addition, these patients are more prone to have resistant pathogens as the cause of their UTIs, including extended-spectrum β-lactamase-positive *Enterobacteriaceae*, fluoroquinolone-resistant uropathogens, carbapenem-resistant *Enterobacteriaceae*, and vancomycin-resistant *Enterococci*. Susceptibility to UTIs increases with longer duration and greater severity of diabetes. High urine glucose content and defective host immune factors predispose to infection. Hyperglycemia causes neutrophil dysfunction by increasing intracellular calcium levels and interfering with actin and, thus, altering diapedesis and phagocytosis [32]. Various impairments in the immune system, including humoral, cellular, and innate immunity may contribute in the pathogenesis of UTIs in diabetic patients. Bacteria have ability to thrive in the presence of elevated blood sugar, and, in addition, a hyperglycemic state negatively affects the body's ability to respond to antimicrobial therapy. In our study 7/14 *Klebsiella* UTIs patients had type 2 diabetes as co-morbidity for CKD. The

association of diabetes-CKD further favors UTIs.

In a study performed in a tropical region, *K. pneumoniae* was found to the most frequent bacterial etiological agent in UTIs, after *Escherichia coli*, both isolated microorganisms being highly resistant to ampicillin, trimethoprim/sulfamethoxazole, doxycycline, amoxicicline/clavulanic acid, whereas *Klebsiella* demonstrated also to be highly resistant to cefuroxime, ceftriaxone and gentamycin [33].

An Indian study, found that most of the *Klebsiella* strains in UTIs were susceptible to amikacin. In our study, *K. pneumoniae* isolated from the urine of CKD patients revealed that, from 14 strains tested, 12 were susceptible to amikacin. Rare use of this antibiotic in our region may explain the maintenance of susceptibility [34]. A study in Jordan highlighted that all isolates from the UTI of *Klebsiella* were resistant to at least one antibiotic [35]. In our study, most *Klebsiella* strains were resistant to more than three antibiotics.

Tazobactam in combination with piperacillin has an excellent clinical efficacy in various infections [20]. Tazobactam is a promising beta-lactamase inhibitor which has its own antibiotic activity. In our study, if the resistance to amoxicillin with clavulanic acid was significant, the association of piperacillin with tazobactam was found to be effective in the percentage of 50% and cefoperazone with sulbactam (85.71%).

A recent Taiwanese study revealed in the last decade a decreased susceptibility of *Klebsiella* to most antibiotics, especially third generation cephalosporins and fluoroquinolones [37]. Fluoroquinolones appear to be drugs of choice for the treatment of pyelonephritis and cystitis in patients with renal dysfunction. Theoretically, ciprofloxacin would appear to be the preferred fluoroquinolone in CKD. It is secreted as well as filtered, and has good tissue penetration. A broad spectrum cephalosporin such as ceftriaxone may also be considered as an alternative to ciprofloxacin in chronic kidney failure, but *K. pneumoniae* in our study shows a high degree of resistance to this antibiotic (8/13-61.54% resistant strains).

Fosfomycin is increasingly used for empiric treatment of urinary tract infection in the absence of routine drug susceptibility testing [38]. Fosfomycin is a phosphonic acid derivative with antibacterial activity against a wide range of gram-negative pathogens and some gram-positive pathogens [24]. The antibacterial spectrum of fosfomycin includes the most of the enteric gram-negative bacteria, but with a considerably higher MIC for *Klebsiella* sp [38]. In our study, a relatively large number of *K. pneumoniae* is resistant to fosfomycin (50%), probably as a consequence of its frequent use in uncomplicated urinary tract infections.

Patients with chronic kidney failure, up to a creatinine clearance of 20mL/min, can be expected to have still sufficiently high urinary concentrations of fosfomycin, and treatment of cystitis may be justified from pharmacokinetic/ pharmacodynamic point of view. Single oral dose therapy with fosfomicin is recommended for treatment and prophylaxis of uncomplicated UTIs, not only in premenopausal, but also in post-menopausal elderly, otherwise healthy women above 65 years of age [39]. Our study revealed that increased use of fosfomycin trometamol in recent years has probably led to an increase in resistance to this antibiotic.

The death of the two patients with CKD (14.28%) in the study group was favored by the presence of severe kidney failure, advanced age, CVD complications and *Klebsiella pneumoniae* UTIs.

The multiple resistance to antibiotics of the *Klebsiella pneumoniae* strains was correlated with the advanced age of the patients, the presence of diabetes in four cases, advanced renal failure with high serum urea and creatinine levels, and male gender.

Conclusions

Klebsiella pneumoniae strains isolated from urine in UTI patients with CKD are the most important uropathogenic microorganisms, after *Escherichia coli.*

UTIs due to *K. pneumoniae* are favored by the presence of CKD, with increased blood urea, in turn the CKD evolution to the final stages is accelerated by UTI.

Although the percentage of urinary infections with *K. pneumoniae* is reduced in the case of uropathogenic isolates from patients with advanced CKD stages, isolated strains are multiresistant in more than four classes of antibiotics.

The treatment of UTIs caused by *K. pneumoniae* with trimethoprim/ sulfamethoxazol, nitrofurantoin, first generation of cephalosporins, and even the combination of broad spectrum penicillin (amoxicillin) with beta-lactamase inhibitor (clavulanic acid) has no more favorable effect on patients with UTIs and CKD, due to high resistance.

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UTIs with multiresistant *K.pneumoniae* have a high prevalence in older subjects with CKD. Renal insufficiency with uraemia increases the severity of urinary infection with frequent recurrences and worsening of kidney disease.

It appears that the aggressiveness of the bacteria increases with the increase in antibiotic resistance mechanisms and the degree of renal insufficiency in CKD.

In CKD, UTI recurrences with *K. pneumoniae* occur due to alterations of immune defense mechanisms, especially with comorbidities, such as diabetes. UTI recurrences increase bacterial resistance to antibiotics by selecting multiresistant strains.

The fatal progression of patients with end-stage CKD is favored by CVD, but also possible to *Klebsiella* infection and advanced age.

For UTIs treatment in CKD patients with high degrees of renal impairment as first choice may be a fluoroquinolone (ciprofloxacin), and in severe and persistent forms, piperacillin/ tazobactam or cefoperazone/ sulbactam. Imipenem cilastatin, a carbapenem, may be retained as a reserve antibiotic in urosepsis. Aminoglycosides are poorly used due to nephrotoxicity, especially in advanced CKD stages (stages 4 and 5 of kidney failure).

This study had the approval of the local Hospital Ethics Committee.

This study was designed to fully protect the anonymity of patients, confidentiality of data, respecting principles of the contemporary version of the Declaration of Helsinki.

The limits of the study are represented by the fact that is a retrospective study, there was a short time period for assessment of UTIs with *K. pneumoniae* in patients with CDK, and not use the similar antibiotics for susceptibility testing in case of relapses.

Contributors

Authors designed the study strategy, reviewed the literature, performed the laboratory investigations and all authors approved the final version of the manuscript. First three authors performed the laboratory investigations, while the fourth author was involved in immunological comments. Pharmacology problems have been solved by the fifth author. The sixth author carried out the statistical processing. This report is independent research and the authors report no conflicts of interest in this work.

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