BANTAO Journal 2014; 12(1): 27-32

BJ
BANTAO Journal

Original Article

Antibiotic Sensitivity and Resistance Among the Most Common Uropathogens in Kidney Transplant Recipients

Borelli Zlatkov[1], Jean Filipov[1], Emil Paskalev[1], Boyka Markova[2], Yuliya Marteva-Proevska[2] and Alexandar Kolevski[2]

[1]Department of Nephrology and Transplantation, [2]Central Laboratory of Microbiology, University Hospital "Alexandrovska" Sofia, Bulgaria

Abstract

Introduction. Urinary tract infection (UTI) among kidney transplant recipients (KTRs) is one of the most common complications after transplantation. The aim of our study was to analyze the antibiotic sensitivity and resistance of the most common agents causing UTI in Bulgarian KTRs followed up in our Transplant Center.
Methods. We analyzed the antibiotic resistance and sensitivity of the most common strains of bacteria causing UTI in the Bulgarian KTRs, namely class Enterobacteriaceae and Enterococcus spp. We used conventional biochemical methods to identify different strains of uropathogens-miniApi (bioMerieux, France) and BBL Crystal (BD). The antibiotic sensitivity was determined via disc-diffusing method, according to the accepted Bulgarian CLSI standard. We used WHONET, version 5.6 to analyze the antibiotic resistance data.
Results. The total number of tested patients was 366 [males 228, females 138]. The total number of tested urine samples was 829 [positive ones-203), negative samples 606, contaminated 20]. The most commonly detected uropathogens in Bulgarian KTRs were Gram /-/ negative bacteria (63.80%). Of these, 93.28% belonged to the Enterobacteriaceae group, with E. coli, K. pneumoniae and the PPM /Proteus, Providentia, Morganela/subgroup being the most common (54.5%, 19.20% and 16%, respectively).
Gram /+/ positive bacteria were detected in 28.09% of the patients, Enterococcus spp being the most commonly isolated-67.79%. In the Enterococcus group, the strains of E. faecalis and E. faecium were the most commonly detected.
The bacteria belonging to Enterobacteriaceae group were most sensitive to carbapenems and aminoglycosides, with sensitivity peaking to almost 100%, whereas they were least sensitive to aminopenicillines [sensitivity below 20%]. The PPM subgroup revealed very high sensitivity to beta-lactamase protected broad spectrum penicillins (Piperacillin/Tazobactam, sensitivity - 90%).
Gram /+/ positive uropathogens were mostly sensitive to Linezolid, Vancomycin, Teicoplanin (100%). These strains were least sensitive to Erythromycin and Tetracicline (17.50%).
Conclusions. Our results were similar to previous studies. The differences detected can be explained with the characteristics of the bacterial strains and the specific practice of each transplant center. Having in mind the possible complications of UTIs, further studies are needed to clarify the problem with antimicrobial resistance in uropathogens and the use of antibiotics after KT.

Key words: kidney transplantation, urinary tract infections, antibiotics, antibiotic resistance and sensitivity

Introduction

Urinary tract infections (UTIs) are the second most common inflammatory disease in humans, coming after the inflammatory diseases of the lungs [1,2]. This is a non-specific, destructive disease of the renal interstitium, pelvis and the urinary tract due to direct bacterial, viral or mycoplasmal invasion, associated with inflammatory reaction from the patient [1].
The most commonly detected etiologic agents are Gram (-) negative bacteria (E.coli, Klebsiela, Proteus, Pseudomonas, Acinetobacter, Serratia), Gram (+) positive agents-Enterococcus spp., Staphylococcus spp., C. trachomatis; fungi (Candida spp.), viruses, tuberculosis [1-4].
UTIs are one of the most frequent complications of kidney transplantation (KT) with prevalence ranging from 30% to 80%. Urinary infection may cause graft dysfunction and may increase the risk for acute rejection [2-4]. Chronic UTIs in kidney transplant recipients (KTRs) have the same characteristics as those in the early post-transplant period, with a slow and chronic development of the symptoms. The treatment is based on similar principles. However, in KTRs there are certain peculiarities. There is a permanent immunosuppressive therapy in-

Correspondence to: Borelli Zlatkov, Clinic of Nephrology and Transplantation, UMHAT "Alexandrovska", 1, Sv. G. Sofiiski str. 1431 Sofia, Bulgaria; Phone: 00 359 2 9230233; E-mail: dok_zlatkov@abv.bg

creasing the risk for incomplete remission of the UTIs, especially in association with other risk factors [3-5]. Additional risk factors are female gender, elderly patients, urethral catheter (used routinely within 2 to 3 days after KT) and anatomical abnormalities of the native kidneys or the graft, diabetes mellitus, urologic procedures [4-6]. The etiologic agents are similar to those in the native kidneys in the common population. However, there is a difference in the prevalence of certain bacterial strains. UTIs in the first months after transplantation are associated with severe pyelonephritis, sepsis, and frequent transformation to chronic UTI. Therefore, they should be treated aggressively. Aggressive therapy means not only the bacterial sensitivity, but the equally important treatment duration. These infections are associated with graft dysfunction and increase the risk of acute rejection [4,7,8]. In cases of rapidly developed urinary infections in the early posttransplant period, associated with sepsis or pyelonephritis, intravenous antibiotic treatment must be initiated, followed by oral antimicrobials according to the bacterial sensitivity for 2 to 6 weeks [8-10]. Long-term therapy is also indicated in patients with predisposing factors for UTI (anatomical abnormalities, neuropathic bladder etc.). Outpatient UTIs developed within 3 months after transplantation should be treated with long oral course-up to 6 weeks [6,11,12]. Short antibiotic courses (10 to 14 days) are associated with high incidence of recurrence. Benign UTIs 3 to 6 months after KT have similar prognosis to those in the general population, therefore they can be treated with shorter oral courses (10 to 14 days). Single-dose therapy is not recommended in KTRs as it leads to unsatisfactory results (usually relapse). The presence of predisposing factors for UTI, especially hydronephrosis and urologic manipulation, may be an indication for prophylaxis [9,13,14].
The choice of the most adequate antibiotic is of utmost importance for the outcome of the UTI treatment [2,3,15]. Therefore, the study of the etiologic agents and their sensitivity to the most commonly used antimicrobials are major factors determining the plan of the treating physician. The aim of our study is to present the sensitivity/resistance of the most commonly detected etiologic agents for UTIs after KT to the most frequently used antibiotics.

Material and methods

A total of 366 KTRs, followed-up in our Transplant Center, were enrolled in our study from 1.01.2012 till 31.08.2012. Males predominated (n=228), and 138 were females. The total number of urine samples was 829, positive were 203 (24.29%); 606 were negative samples (73.10%); contamination was detected in 20 samples (2.41%).
The most commonly detected bacteria in Bulgarian KTRs were Gram /-/ negative (63.80%). Of these, 93.28% belonged to the Enterobacteriaceae group; with E. coli, K. pneumoniae and the PPM /Proteus, Providentia, Morganela/subgroup being the most common (prevalence of 54.5%, 19.20% and 16%, respectively). Gram /+/ positive bacteria were detected in 28.09% of the patients, Enterococcus spp being the most commonly isolated-67.79%. In the Enterococcus group, the strains of E. faecalis and E. faecium were the most commonly detected.
The immunosuppressive agents used in the KTRs were steroids, mycophenolate mofetil (MMF), Mycophenolate sodium (M-Na), cyclosporine A, Tacrolimus, Everolimus, Sirolimus in different combinations.
Urinary tract infection was defined as the presence of significant bacteriuria, combined with dysuria, pyrexia, hydronephrosis. Other routine tests were performed in order to optimize the therapy. The treatment was performed in out-patient or in-patient setting according to the individual characteristics of each patient. Additional laboratory and imaging studies were performed in order to assess kidney graft function, viral status (testing for hepatatis B, hepatitis C and cytomegalovirus infection).
Around 210 bacterial strains were isolated. In the cases where a given strain was detected more than once in a given patient the doubling results were excluded from the study.
We used conventional biochemical methods to identify different strains of uropathogens-automatic and semi-automatic biochemical identification systems-miniApi (bioMerieux, France) and BBL Crystal (BD). The antibiotic sensitivity was determined via disc-diffusion method, according to the accepted Bulgarian CLSI standard. We used WHONET, version 5.6 to analyze the antibiotic resistance data [16].
Microsoft Excel was used for statistical analysis. Variation and correlation analyses were applied, together with tables to compare the results and rank analysis to identify outliers.

Results

The total number of tested patients was 366 [228(62.30%) males, 138(37.70%) females]. The total number of tested urine samples was 829 [positive-203(24.29%), negative-606(73.10%), contaminated-20(2.41%)]. The most commonly detected bacteria in KTRs in our study were Gram /-/ negative (63.80%). Of these, 93.28% belonged to the Enterobacteriaceae group, with E. coli, K. pneumoniae and the PPM /Proteus, Providentia, Morganela/subgroup being the most common (prevalence of 54.5%, 19.20% and 16%, respectively).
Gram /+/ positive bacteria were detected in 28.09% of the patients, Enterococcus spp being the most commonly isolated-67.79%. In the Enterococcus group, the strains of E. faecalis and E. faecium were the most commonly detected.

Enterobacteriacee group

The most commonly isolated bacteria in our study (Enterobacteriacee) showed the highest sensitivity (S)

to Imipenem (99.20%), with resistance (R) rate of only 0.80%. Similar results were found for Meropenem (S 99.20%, R 0.80%), and for aminoglycosides (Amikacin, S 93.60%, R-6.40%).
High sensitivity was also detected for β-lactamase protected broad spectrum penicillins (Piperacillin-Tazobactam, S 84.80%, R 15.2%). For the cephalosporins tested (Ceftazidime, Cefotaxim, Cefoxitin) the results were the following: sensitivity 73.6%, 69.6%, 76%, whereas for the resistance rates the results were: 26.4%, 30.4%, 24%, respectively.
The sensitivity to Trimetoprim/Sulfametoxasol was 50.40%, and resistance rate was 49.60%. For ciprofloxacin the figures were 57.6% (S) and 42.40% (R). The least sensitivity in this group was detected for aminopenicillins (S 19.20%, R 80.80%).
The results for Enterobacteriaceae class are summarized in Figure 1.

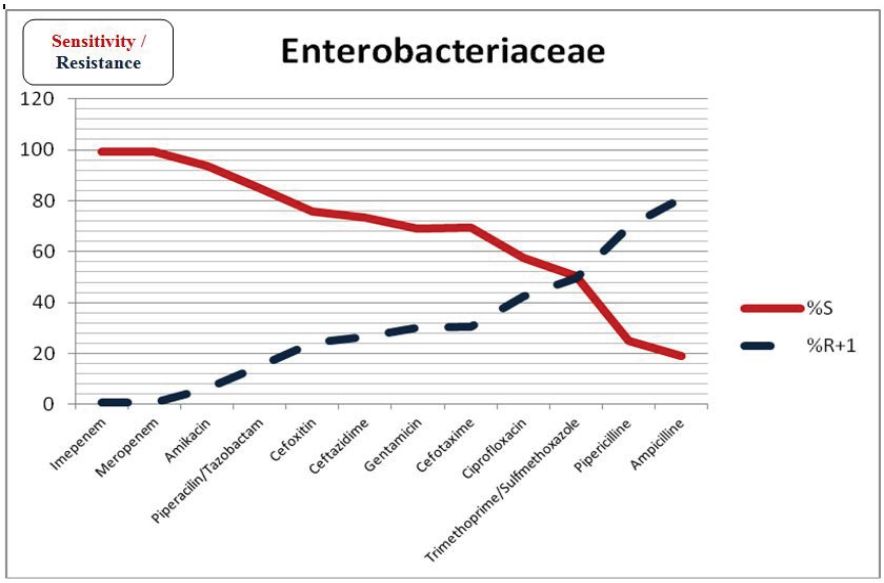

Fig. 1. Antibiotic sensitivity and resistance of the Enterobacteriaceae class

E. coli

E. coli were the most commonly detected members of the class Enterobacteriaceae. These microorganisms revealed 100% sensitivity to carbapenems (Imipenem amd Meropenem). Sensitivity to Amikacin was 97.1%, with resistance rate close to 3%.
High sensitivity was also found for β-lactamase protected broad spectrum penicillins [(Piperacillin/Tazobactam), S 92.6%].
The sensitivity rate of E. coli for second generation cephalosporins (Cefoxitin) peaked to 97.1%, with R of 3%. For Ceftazidime and Cefotaxim the figures were: S 85.3% and 80.9%; R 14.7% and 19.1%, respectively. Trimetoprim/Sulfametoxasol revealed S 64.7%, R 45.6% whereas for Ciprofloxacin E.coli's sensitivity was 64.7% (R 35.3%). The lowest sensitivity rate was established for aminopenicillins [(Ampicillin), S 27.9%, R 72.15].
The results for E. coli antibiotic resistance are depicted in Figure 2.

K. pneumoniae

We established 100% S of K. pneumoniae to carbapenems and 87.5% sensitivity to aminoglycosides (Amikacin). High S was detected also for Cefoxitin (75%, R 25%), moderate S for Piperacillin/Tazobactam (62.5%, R 37.5%). For Ceftazidime and Cefotaxim the sensitivity dropped to 45.8% for both antimicrobials. Similar findings were found for Ciprofloxacin (S 45.8%, R 54.2%) and Trimetoprim/Sulfametoxasol (S 37.5%, R 62.5%). Aminopenicillins (Ampicillin) showed the lowest sensitivity (S 0%, R 100%). The results for K. pneumoniae are shown in Figure 3.

The PPM (Proteus, Providencia, Morganella) subgroup

Again the highest S was detected for carbapenems and Amikacin (S peaking to 95%). Beta-lactamase protected broad spectrum penicillins (Piperacillin/Tazobactam) come second with S 90%, R 10%. For Ceftazidime and Cefotaxim sensitivity rate was 65% and 55%, respectively. Second generation cephalosporins had higher resistance among this subgroup (S 45%, R 55%) compared to third generation cephalosporins. The sensitivity rate dropped further for Ciprofloxacin (S 40%, R60%), Trimetoprim/Sulfametoxasol (S 35%, R 65%), Ampicillin (S 30%, R 70%). The lowest S in PPM subgroup was detected for Tetracycline (S 0%, R 100%). The results are summarized in Figure 4.

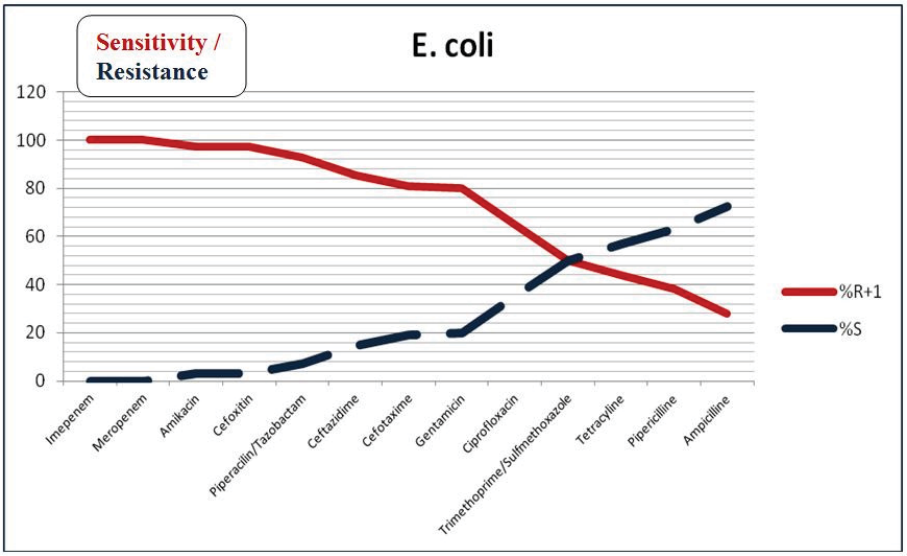

Fig. 2. Antibiotic sensitivity and resistance of E. coli

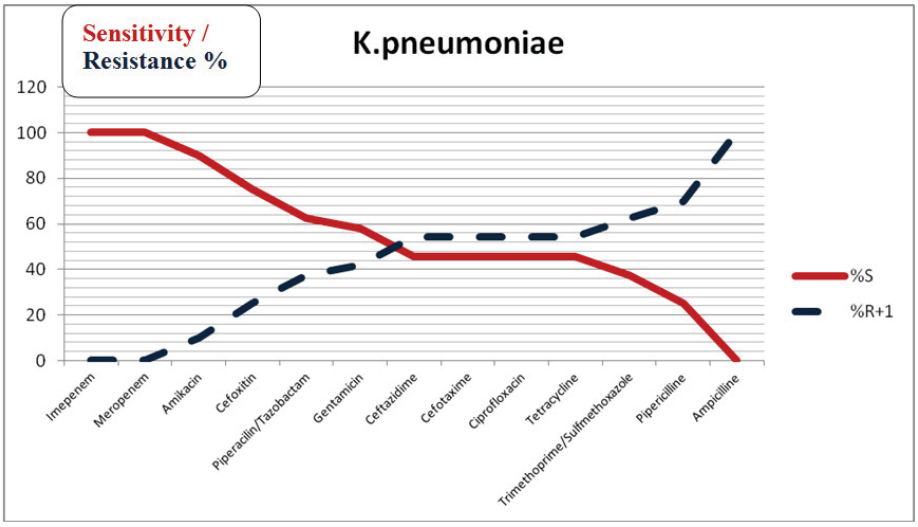

Fig. 3. Antibiotic sensitivity and resistance of K. pneumoniae

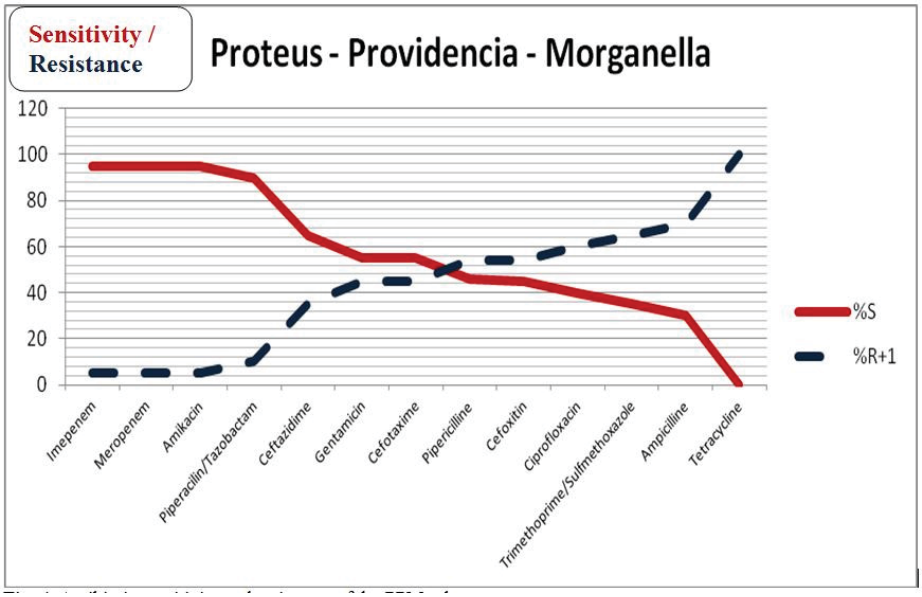

Fig. 4. Antibiotic sensitivity and resistance of the PPM subgroup

Gram /+/ uropathogens

The most commonly detected Gram positive bacteria causing UTIs in our cohort of patients were Enterococcus spp., presented by E. faecalis and E. faecium. They showed highest S to Linezolid, Vankomycin and Teicoplanin (S 100%). Ampicillin came second with S of 80%, R of 20%. Relatively low S was detected for Ciprofloxacin (S 35%, R 65%). The highest resistance was detected for Erythromycin (S 15%, R 85%) and Tetracycline (S below 17.5%). The results for Enterococcus spp are shown in Figure 5.

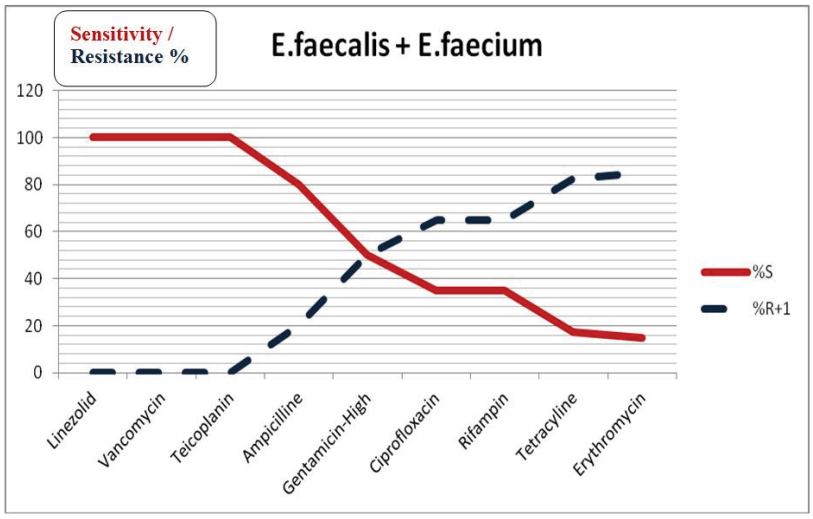

Fig. 5. Antibiotic sensitivity and resistance of E. faecalis and E. faecium

Choosing the best antimicrobial is of vital importance for the outcome in UTIs. Therefore studying of the uropathogens and their sensitivity to the most commonly used antibiotics is fundamental in the treatment strategy of the physician.

UTIs in KTRs may be asymptomatic due to the immunosuppressive treatment, and may evolve to acute pyelonephritis and sepsis, thus making UTIs one of the major factors for decrease in graft function and acute rejection. Therefore, the best choice and the most adequate antibiotic treatment are of utmost importance.

The use of long-term antimicrobial prophylaxis and treatment in KTRs is still under discussion.

Discussion

The urinary tract infections (UTIs) are the most common infections after kidney transplantation (KT). The high prevalence is due to a broad spectrum of factors: immunosuppressive agents, in-dwelling urinary catheters and stents, surgical manipulations, UTIs prior to KT, rejection episodes, cadaver donors.

Our findings confirm the high prevalence of UTIs-24.9% of our KTRs were detected with urinary infection. Our results, however, are lower compared to 30-80% rate established by other authors [2,3,8], which can be explained with the strict follow-up protocol, the prophylaxis and adequate treatment of this type of complication.

The high carbapenem sensitivity detected for the class Enterobacteriaceae bacteria (100%) indicated a low incidence of highly resistant strains. This might be explained by the adequate use of antimicrobials belonging to other classes, thus leaving carbapenems for life threatening, highly resistant UTIs.

The high sensitivity of second, third and fourth generation of cephalosporines coupled with their low cost and low nephrotoxicity [5,7] makes them antibiotics of choice in KTRs, and their utilizing in longer antimicrobial courses.

Gram-negative bacteria (E. coli in particular) had higher sensitivity to second generation cephalosporins than to third and fourth generation. This enables the transplant team to use these antibiotics for treatment of UTIs in the early post-transplant period as well as for oral prophylaxis.

We established medium E. coli sensitivity to Ciprofloxacin (64.7%), thus questioning the idea, that Ciprofloxacin is the antimicrobial of choice in E. coli-caused UTIs [7,8]. Having in mind the high cephalosporin sensitivity of E. coli in our study, we can assume that Ciprofloxacin/cephalosporins can be used in E. coli-UTIs, which definitely broadens our therapeutic armamentarium.

Due to their high nephrotoxicity, aminoglycosydes are used rarely in the treatment of UTIs. This can explain the high sensitivity of Gram-negative uropathogens to Amikacin, peaking up to 90-100%. We firmly believe that aminoglycosides can be used for the treatment of UTIs in KTRs with the adequate dose adjustment and strict follow-up of the kidney function. Our experience proves this approach to be a low risk one. Aminoglycosides offer additional options for antibiotic treatment, reducing further the risk of development of highly resistant bacterial strains.

Our study revealed medium to high resistance of the most common Gram-negative uropathogens to Trimetoprim/Sulfametoxazol (R peaking up to 50%) probably

due to its wide use for Pneumocystis jirovecii prophylaxis. The low sensitivity rate makes the use of Trimetoprim/Sulfametoxazol for UTI prophylaxis highly disputable, in contrast to the recommendations of other authors [9,14,17,18]. However, when indicated, Trimetoprim/ Sulfametoxazol can be used in the routine clinical practice.
The sensitivity to Linezolid, Vancomycin, Teicoplanin among Gram-positive bacteria reached 100%, thus making these antimicrobials the drugs of choice in severe and resistant UTIs after KT.
In addition, high sensitivity to aminopenicillins (80%) was detected in Gram-positive uropathogens. Having in mind their low cost, aminopenicillins can be used as an antibiotic of choice in Gram-positive UTIs. This group is widely used in our daily practice both intravenously and orally.

Conclusions

Our findings were similar to previously reported studies. The differences detected can be explained with the characteristics of the bacteria isolated and the specific practice of each transplant center. Creating protocols for the treatment of UTIs broadens the spectrum of antibiotics of choice and reduces the risk for antibiotic resistance. Further studies are needed to clarify the problem with antimicrobial resistance in uropathogens and the use of antibiotics after KT.

Conflict of interest statement. None declared.

References

1. Gruev I. Urinary Tract Infections. In*: Clinical Nephrology, Medicine and Sports.*1990; 213-232.
2. Paskalev E, Gicheva M, Mateva P, *et al*. Urinary tract infections after kidney transplantation (Abstract). *Nephrol Dial Transplant* 2002; 14; 8.
3. Rubin RH. Infectious disease complications of renal transplantation. *Kidney Int* 1993; 44: 221-236.
4. Saeman M, Horl WH. Urinary tract infection in renal transplant recipients. *Eur J Clin Invest* 2008; 38(Suppl 2): 58-65.
5. Kubak MB, Holt CD. Infectious Complications in Kidney Transplantation and their Management. In: *Handbook of Kidney Transplantation, ed. G. M. Danovitch, 2 ed., Boston, A Little, Brown;* 1996; 187-213.
6. Green H, Rahamimov R, Goldberg E, *et al*. Consequences of treated versus untreated asymptomatic bacteriuria in the first year following kidney transplantation: retrospective observational study. *Eur J Clin Microbiol Infect Dis. Springer-Verlag* 2013; 32: 127-131.
7. Rubin RH, Tolkoff-Rubin NE. Antimicrobial strategies in the care of organ transplant recipients. *Antimicrob Agents Chemother* 1993; 37: 619-624.
8. Maraha B, Bonten H, van Hooff H, *et al*. Infectious complications and antibiotic use in renal transplant recipients during a 1-year follow-up. *Clin Microbiol Infect* 2001; **7**: 619-625.
9. Fox BC, Sollinger HW, Belzer FO, Maki DG. A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy,absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. *Am J Med* 1990; 89: 255-274.
10. Martinez-Marcos F, Cisneros J, Gentil M, *et al*. Prospective study of renal transplant Infections in 50 consecutive patients. *Eur J Clin Microbiol Infect Dis* 1994; 13: 1023-1028.
11. Nicolle LE, Bradley S, Colgan R, *et al.* Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005; 40: 643-654.
12. Samra Z, Ofir O, Lishtzinsky Y, *et al*. Outbreak of carbapenem-resistant Klebsiella pneumoniae producing KPC-3 in a tertiary medical centre in Israel. *Int J Antimicrob Agents* 2007; 30: 525-529.
13. Hernandes PG, Morales JM, Prieto C, *et al*. Usefulness of norfloxacine prophylaxis in late recurrent urinary tract infection after renal transplantation. *Nefron* 1990; 54:193-194.
14. Hibberd PL, Tolkoff-Rubin NE, Doran M, *et al.* Trimethoprim-sufamethoxazole compared with ciprofloxacin for the prevention of urinary tract infection in renal transplant recipients. *Online J Curr Clin Trials* 1992; Doc No 15: [4083 words; 46 paragraphs].
15. Moradi M, Abbasi M, Moradi A, *et al.* Effect of antibiotic therapy on asymptomatic bacteriuria in kidney transplant recipients. *J Urol* 2005; 2: 32-35.
16. Clinical and Laboratory Standards Institute. 2010. Performance Standards for Antimicrobial Susceptibility Testing. Sixteenth Informational Supplement. Approve standard M100-S20. CLSI, Wayne, Pennsylvania, USA.
17. Dummer JS. Pneumocystis carinii infections in transplant recipients. *Semin Respir Infect* 1990; 3: 50-57.
18. Nicolle LE. Asymptomatic bacteriuria: when to screen and when to treat. *Infect Dis Clin North Am* 2003; 17: 367-394.