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Clinical significance of asymptomatic bacteriuria during first year after renal transplantation.

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Introduction:

Despite advances in prophylaxis and treatment infections remain major complications in renal transplant (RTx) population with urinary tract being the most common infection site. The prevalence of urinary tract infections (UTIs) during the first year post-transplant is up to 60% in retrospective studies with asymptomatic bacteriuria (AB) as the most predominant form. The general assumption is that AB is benign. Still, the paucity of symptoms might be attributable to immunosuppression with actual ongoing inflammation of unrecognized significance. In one small study kidney transplant patients with asymptomatic bacteriuria had elevated urine IL-8 level and the authors hypothesized that this phenomenon may reflect impaired immune response to bacterial infection and occult inflammatory process in urinary tract. Even so, the true impact of AB on patient and graft outcomes so far has not been established. This might be why so far there are no evidence-based guidelines for the screening and treatment of AB in this population. It seems crucial to single out patients most susceptible to UTIs, especially recurrent, symptomatic infections and to note most effective prophylaxis and treatment measures. Therefore the aim of the study was to evaluate the incidence, microbiology, risk factors for AB and the influence of AB on long-term renal graft function.

Patients and Methods:

We performed a retrospective cohort study reviewing the medical records of patients who received a renal transplant at Gdańsk Transplantation Centre from 1st January 2007 to 31st December 2009 (n=237). Twenty three patients transferred to other transplantation centres after one month from RTx were excluded from analysis. We analyzed urine cultures with reference to clinical data. We compared demographics and clinical data of patients without UTIs and suffering from UTIs. The following variables were considered: aetiology of end-stage renal disease, age, sex, comorbidity (estimated with the use of Charlson Comorbidity Index (CCI)), recurrent UTIs before RTx, dialysis type, pretransplant dialysis time, repeated transplantation, episodes of acute rejection (AR), acute tubular necrosis (ATN), delayed graft function (DGF), use of a double-J ureteral stent, type of immunosuppression used (cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil/sodium), induction therapy with monoclonal (basiliximab) and polyclonal antibodies (antithymocyte globulin ATG), CMV infections. To assess renal allograft function we used serum creatinine concentrations and MDRD estimated glomerular filtration rate (abbreviated MDRD eGFR) recorded every three months 1 – 24 months posttransplant.

Definitions of UTIs

All UTIs were classified into one of four following categories:

- asymptomatic bacteriuria (AB) - isolation of bacterial strain in quantitative counts $\geq 10^5$ colony-forming units (CFU) in a clean-catch voided urine specimens in the absence of any symptoms of lower or upper UTI (including leukocyturia) (in women in two consecutive specimens, the second obtained after at least 24 hours) or $< 10^5$ CFU in patients treated with antibiotics or $\geq 10^2$ CFU in a single catheterized urine specimen
- lower UTI - was diagnosed in the presence of bacteriuria and clinical manifestations of dysuria, frequency or urinary urgency and fever $< 38^\circ\text{C}$ in the absence of AGPN criteria
- upper UTI (AGPN) - was defined by the presence of significant bacteriuria, fever $> 38^\circ$ +/- graft pain +/- acute graft function impairment
- Urosepsis - the diagnosis was made when simultaneous positive blood and urine cultures were obtained with the isolation of the same bacterial strain

Statistical analysis

All analyses were performed using R language. Continuous variables were compared by using Student's unpaired t test or the Mann-Whitney U test and proportions with χ^2 test or Fisher's exact test when appropriate. Logistic regression analyses were performed to find independent risk factors for UTIs. Statistically significant variables in the univariate analysis were introduced in a multivariate model based on forward stepwise logistic regression. Associations are given as odds ratios (ORs) with a 95% confidence interval (95% CI). Statistical tests were two-sided with significance less than 0.05.

Results:

209 RTx recipients (85 women and 124 men) with mean age of 46.38 ± 14.05 years and mean dialysis vintage of 26.56 ± 30.61 months.

The aetiologies of end-stage renal failure: primary glomerulonephritis (70/33.5%), autosomal dominant polycystic kidney disease (ADPKD) (32/15.3%), diabetic nephropathy (23/11.0%), hypertensive nephropathy (17/8.1%), tubulointerstitial nephritis (21/10.1%), lupus nephritis (3/1.4%), others (6/2.9%), unknown aetiology (37/17.7%)

23 patients underwent second RTx, 3 patients – third RTx.

Mode of RRT before RTx: 155 (66%) patients were on maintenance haemodialysis (MHD) before the transplantation, 46 (14%) were on chronic peritoneal dialysis (CPD), including 17 patients who were treated consecutively with both MHD and CPD (8%), another 25 patients underwent pre-emptive transplantation (12%)

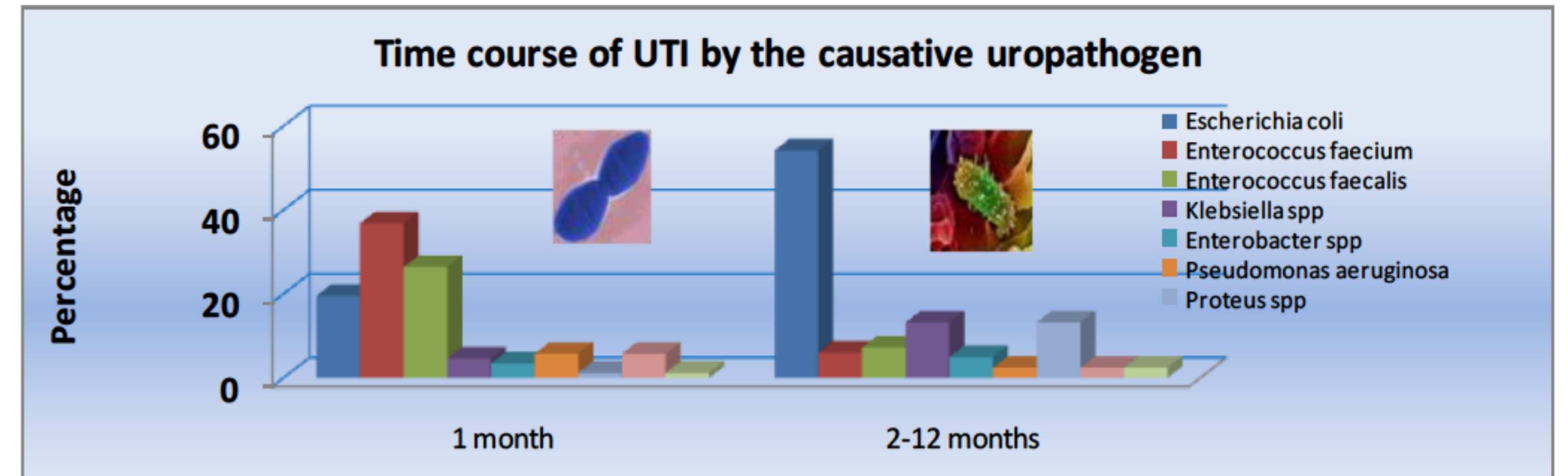
All patients received grafts from deceased donors, apart from only four from a living related donor.

Immunosuppression: tac n=131, CsA n=78, MMF n=202, sirolimus n=6, everolimus n=4, induction with ATG =14 and with basiliximab =5.

- More than half of AB episodes were diagnosed during the first month post-transplant and the most frequently isolated uropathogen was *Enterococcus faecium* (36,8%, n=32). Beginning from the second month the bacterium most frequently found in urine cultures was *Escherichia coli* (54,2%, n=45). (Figure 1)
- When we compared patients with only AB episodes and patients with at least one symptomatic UTI to patients without any UTIs, history of recurrent UTIs before RTx, use of induction and episodes of acute rejection were significantly more common in symptomatic UTI group. (Table 1)
- Female gender, use of induction, comorbidity measured by Charlson Comorbidity Index, history of acute rejection and CMV infection were risk factors for developing AB in univariate analysis and were similar to risk factors for developing any kind of UTI. (Table 2)
- 46 out of 83 patients with AB also developed symptomatic UTIs. AB in multivariate analysis was an independent risk factor for symptomatic UTIs (both lower and upper UTIs) and in univariate analysis it was a risk factor for acute graft pyelonephritis and urosepsis.

Conclusions:

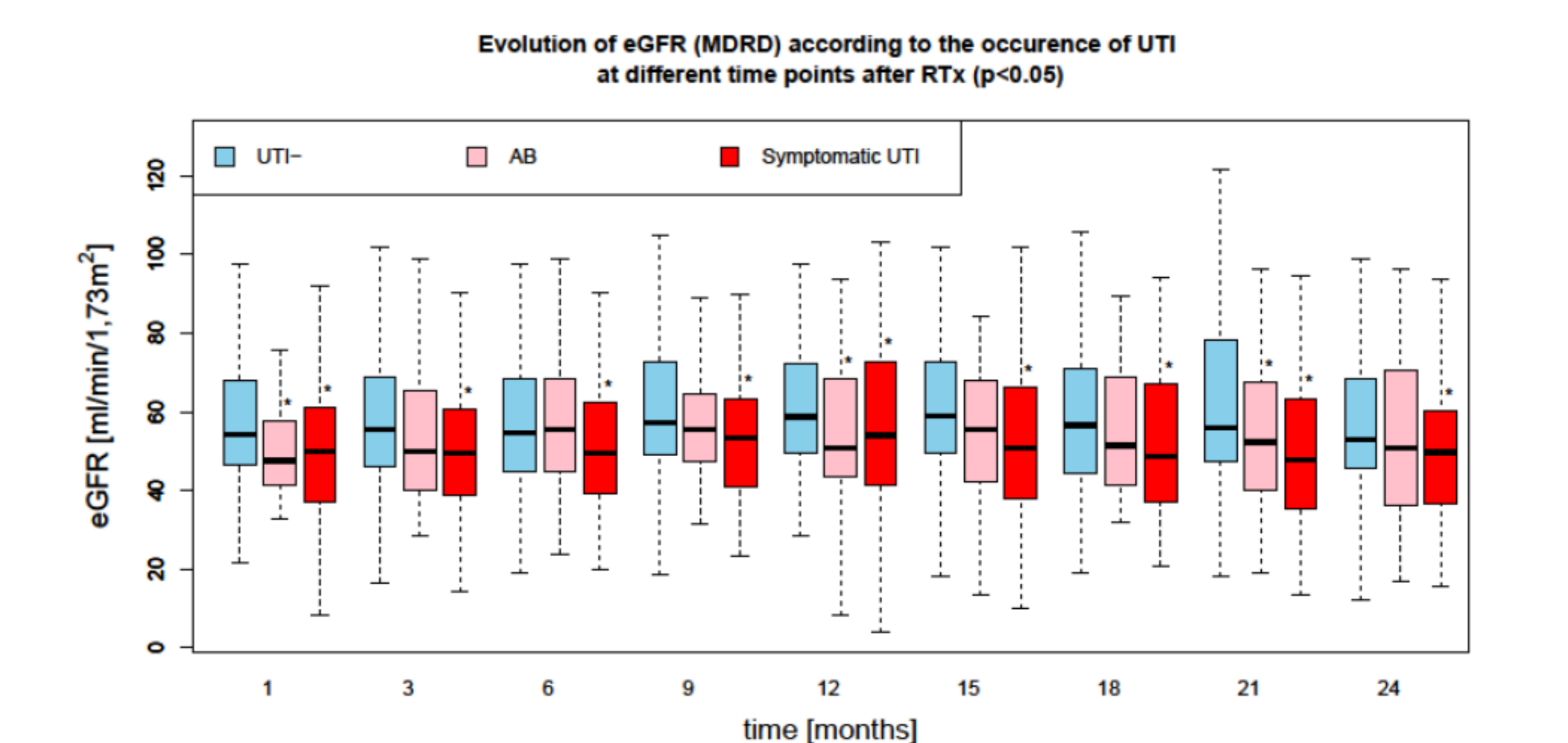
- Asymptomatic bacteriuria is the most common form of UTIs.
- Escherichia coli* and *Enterococcus faecium* are predominant pathogens.
- Recurrent AB episodes, may be considered either a risk factor or a marker of increased susceptibility to symptomatic infections.
- It seems that patients with history of recurrent UTIs before RTx and exposed to greater immunosuppression due to use of induction and episodes of acute rejection are at risk of developing serious symptomatic infections and therefore could benefit most from systematic screening and proper prophylaxis including treatment of AB.
- AB and symptomatic UTI do not affect renal graft function prognosis



Variable, n (%)	UTI - (n=98)	AB (n=37)	symptomatic UTI + (n=74)	p
Age (years)	44.93 ± 13.52	49.16±14.7	46.9±14.36	¹ 0.15 ² 0.34 ³ 0.56
Gender (F/M)	16/82 (16.3%/83.7%)	22/15 (59.5%/40.5%)	47/27 (63.5%/36.5%)	¹ <0.001 ² <0.001 ³ 0.7
Comorbidity (CCI) (points)	3.73±1.78	4.7±1.75	4.42±2.07	¹ 0.002 ² 0.03 ³ 0.3
Recurrent UTIs before RTx	6 (6.1%)	1 (2.7%)	20 (27%)	¹ 0.4 ² 0.001 ³ 0.002
HD before RTx	78 (79.6%)	30 (81.1%)	47 (63.5%)	¹ 0.85 ² 0.02 ³ 0.06
PD before RTx	20 (20.4%)	9 (24.3%)	17 (23%)	¹ 0.36 ² 0.68 ³ 0.87
Dialysis vintage before RTx (months)	23.94±25.39	27.05±25.44	29.81±38.39	¹ 0.47 ² 0.9 ³ 0.47
Second RTx	10 (10.2%)	3 (8.1%)	13 (17.6%)	¹ 0.7 ² 0.16 ³ 0.18
AR	19 (13.4%)	13 (35.1%)	27 (36.5%)	¹ 0.06 ² 0.01 ³ 0.89
ATN	17 (17.4%)	4 (10.8%)	15 (20.3%)	¹ 0.35 ² 0.63 ³ 0.21
DGF	27 (27.6%)	13 (35.1%)	20 (27%)	¹ 0.4 ² 0.94 ³ 0.38
Double-J catheter	56 (57.1%)	23 (62.2%)	48 (64.9%)	¹ 0.6 ² 0.3 ³ 0.8
CsA	42 (42.9%)	10 (27.0%)	26 (35.1%)	¹ 0.09 ² 0.3 ³ 0.4
Tac	57 (58.2%)	26 (70.3%)	48 (64.9%)	¹ 0.2 ² 0.37 ³ 0.57
MMF/MPS	95 (96.9%)	36 (97.3%)	71 (95.9%)	¹ 0.9 ² 0.7 ³ 0.7
ATG	2 (2.0%)	3 (8.1%)	9 (12.2%)	¹ 0.1 ² 0.07 ³ 0.5
basiliximab	2 (2%)	2 (5.4%)	1 (1.4%)	¹ 0.3 ² 0.7 ³ 0.2
Induction (either ATG or basiliximab)	4 (4.1%)	5 (13.5%)	10 (13.5%)	¹ 0.05 ² 0.03 ³ 1.0
CMV infection	12 (12.2%)	10 (27%)	26 (35.1%)	¹ 0.04 ² <0.001 ³ 0.4

¹ UTI – vs AB, ² UTI – vs symptomatic UTI, ³ AB vs symptomatic UTI

Variable, n (%)	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
Age (years)	1.02 (0.99 – 1.04)	0.76	-	-
Gender (F/M)	5.19 (2.83 – 9.5)	<0.001	4.12 (2.168 – 7.86)	<0.001
Comorbidity (CCI) (points)	1.24 (1.07 – 1.44)	0.005	1.24 (1.05 – 1.47)	0.01
Recurrent UTIs before RTx	1.76 (0.78 – 3.99)	0.17	-	-
HD before RTx	0.85 (0.45 – 1.6)	0.62	-	-
PD before RTx	1.53 (0.79 – 2.98)	0.2	-	-
Dialysis vintage before RTx (months)	1.00 (0.99 – 1.01)	0.3	-	-
Second RTx	1.61 (0.7 – 3.7)	0.26	-	-
AR	2.09 (1.13 – 3.86)	0.018	1.44 (0.71 – 2.95)	0.3
ATN	0.96 (0.46 – 2.01)	0.91	-	-
DGF	1.36 (0.74 – 2.5)	0.32	-	-
Double-J catheter	1.24 (0.7 – 2.21)	0.46	-	-
CsA	0.54 (0.3 – 0.98)	0.04	0.54 (0.28 – 1.05)	0.07
Tac	1.68 (0.93 – 3.04)	0.08	-	-
MMF/MPS	1.67 (0.31 – 8.92)	0.54	-	-
ATG	6.26 (1.68 – 23.38)	0.006	-	-
basiliximab	1.01 (0.16 – 6.46)	0.99	-	-
Induction (either ATG or basiliximab)	3.71 (1.34 – 10.27)	0.01	2.62 (0.82 – 8.34)	0.1
CMV infection	2.16 (1.12 – 4.16)	0.02	1.77 (0.84 – 3.72)	0.13



*p<0.05 compared to UTI-

