Klebsiella spp urinary tract infections during first year after renal transplantation.

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Introduction:

Urinary tract infections (UTIs) are common complications in renal transplant (RTx) recipients with prevalence up to 60% during the first year post-transplant. *Klebsiella* spp belong to Gram-negative, facultative anaerobic, nonmotile and nonflagellated bacilli. These are commensal bacteria of the nasopharynx and gastrointestinal tract. The latter is often the latent source for infections. *Klebsiella* spp with the most often isolated pathogen *Klebsiella pneumoniae* is a well recognized source of nosocomial infections in immunocompromised patients and is also the most common pathogen capable of producing extended-spectrum β-lactamases (ESBL). *Klebsiella* spp is also the most common pathogen in recurrent UTIs during first year after RTx. What is more, it is the second most common Gram-negative causative agent of bloodstream infections in solid organ transplant recipients. Due to multidrug resistance *Klebsiella* spp upper UTIs are serious, even life-threatening problem. Therefore the aim of the study was to assess the risk factors for developing *Klebsiella* spp upper UTIs.

Patients and Methods:

We performed a retrospective cohort study reviewing the medical records of RTx recipients who are under care at Gdańsk Transplantation Centre (n=451). We analyzed urine cultures performed within first 12 months after RTx and recorded all *Klebsiella spp* urinary tract infections. We compared demographics and clinical data of patients without *Klebsiella* spp AGPNs (acute graft pyelonephritis) and those suffering from *Klebsiella* spp AGPNs. 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, pre-transplant dialysis time, repeated transplantation, episodes of acute rejection (AR), acute tubular necrosis (ATN), delayed graft function (DGF), use of a double-J ureteral stent, VUR (vesico-ureteral reflux) or stenosis at vesico-uretreral junction, type of immunosuppression used (cyclosporine, tacrolimus, everolimus, mycophenolate mofetil/sodium), induction therapy with monoclonal (basiliximab) and polyclonal antibodies (antithymocyte globulin ATG), CMV infections.

Definitions of UTIs

All UTIs were classified into one of four following categories:

(1) asymptomatic bacteriuria (AB) - isolation of bacterial strain in quantitative counts ≥ 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 ≥ 10^2 CFU in a single catheterized urine specimen

(2) lower UTI - was diagnosed in the presence of bacteriuria and clinical manifestations of dysuria, frequency or urinary urgency and fever < 38°C in the absence of AGPN criteria

(3) upper UTI (AGPN) - was defined by the presence of significant bacteriuria, fever > 38° +/- graft pain +/- acute graft function impairment

(4) 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 Statistica 10.0. 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.
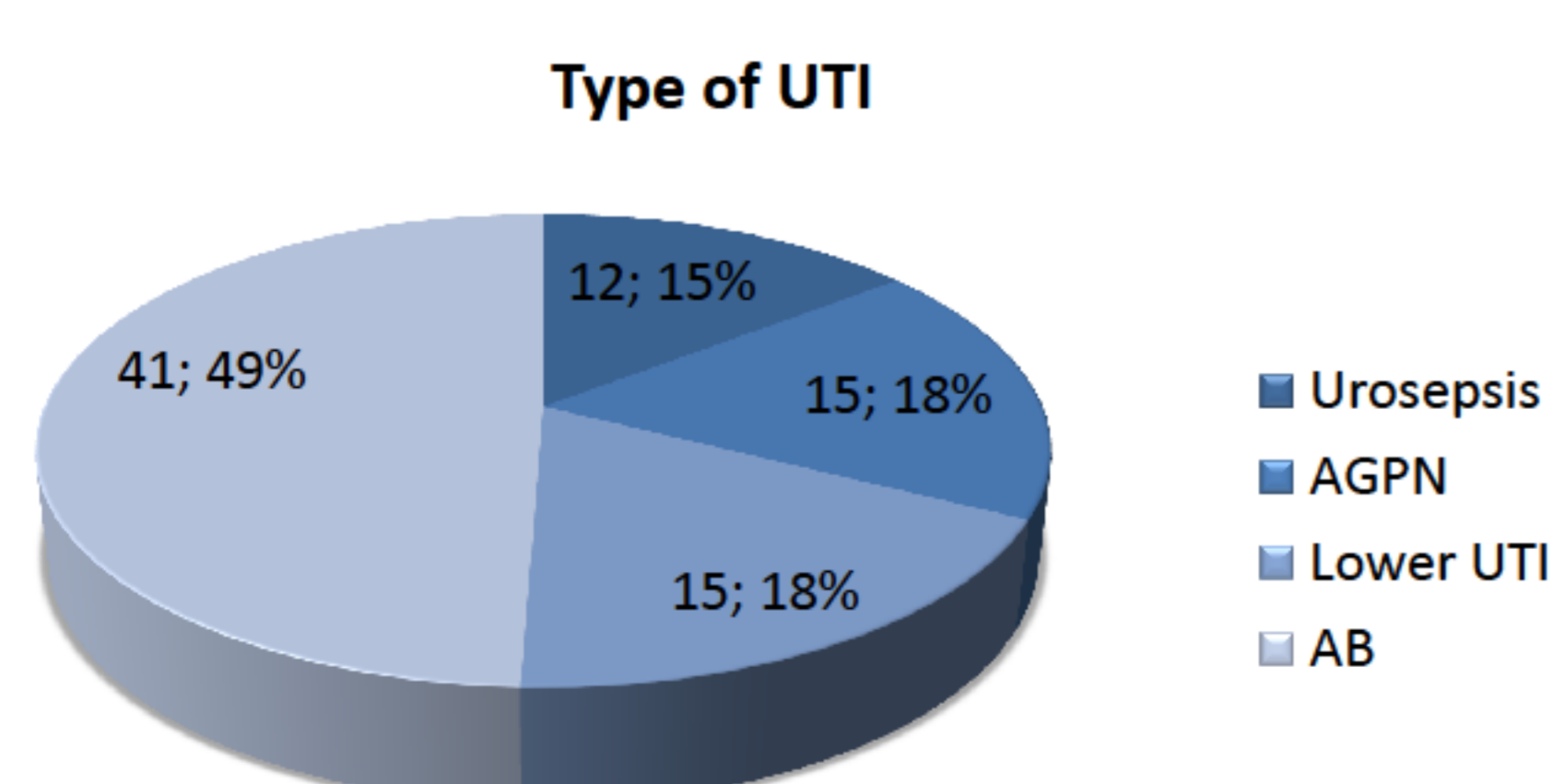
Results:

Type of UTI

12; 15% Urosepsis
15; 18% AGPN
15; 18% Lower UTI
41; 49% AB

Table 1. Demographic and clinical features of the groups

Variable, n (%)	*Klebsiella spp* upper UTI – (n=20)	*Klebsiella spp* upper UTI+ (n=14)	p
Age (years)	49 (23-69)	58.5 (24-71)	0.16
Gender (F/M)	14/6 (70.0/30.0)	5/9 (35.7/64.3)	**0.05**
Comorbidity (CCI) (points)	4.5 (2-9)	5.0 (2-7)	0.42
Recurrent UTIs before RTx	3/17 (15.0/85.0)	3/11 (21.4/71.6)	0.67
HD before RTx	15/5 (75.0/25.0)	12/2 (85.7/14.3)	0.67
PD before RTx	9/11 (45.0/55.0)	3/11 (21.4/78.6)	0.27
Dialysis vintage before RTx (months)	32.5 (1-192)	32.0 (7-96)	0.93
Second RTx	5/15 (25.0/75.0)	4/10 (26.6/71.4)	1.0
AR	6/14 (30.0/70.0)	3/11 (21.4/71.6)	0.7
ATN	5/15 (25.0/75.0)	4/10 (26.6/71.4)	1.0
DGF	7/13 (35.0/65.0)	4/10 (28.6/71.4)	1.0
Double-J catheter	14/6 (70.0/30.0)	9/5 (64.3/35.7)	1.0
CsA	3/17 (15.0/85.0)	3/11 (21.4/78.6)	0.67
Tac	17/3 (85.0/15.0)	11/3 (78.6/21.4)	0.67
MMF/MPS	18/2 (90.0/10.0)	13/1 (92.9/7.1)	1.0
Induction (ATG/basiliximab)	6/14 (30.0/70.0)	3/11 (21.4/71.6)	0.7
CMV infection	6/14 (30.0/70.0)	8/6 (57.1/42.9)	0.16
VUR or stenosis at vesico-uretreral junction	1/19 (5.0/95.0)	6/8 (42.9/57.1)	**0.01**

Characteristics of Klebsiella spp upper UTI+

•Almost 80% of episodes were diagnosed beginning from the second post-transplant month.

•Over 70% of upper *Klebsiella* spp UTI were due to ESBL+ strains.

•There was an increase in the incidence of multidrug resistant bacteria over time: 43% of *Klebsiella* spp strains isolated between 2007-2010 were ESBL (+) and 75% of *Klebsiella* spp were confirmed as ESBL (+) between 2011-2013

•All 34 patients had clinical resolution and negative urine cultures after the treatment of every single episode, however 17 patients required readmissions due to *Klebsiella* spp infection recurrence.

•We had two fatal outcomes during the study period.

Proportion of ESBL+ strains according to the type of UTI

* AB
Lower UTI
AGPN
Urosepsis
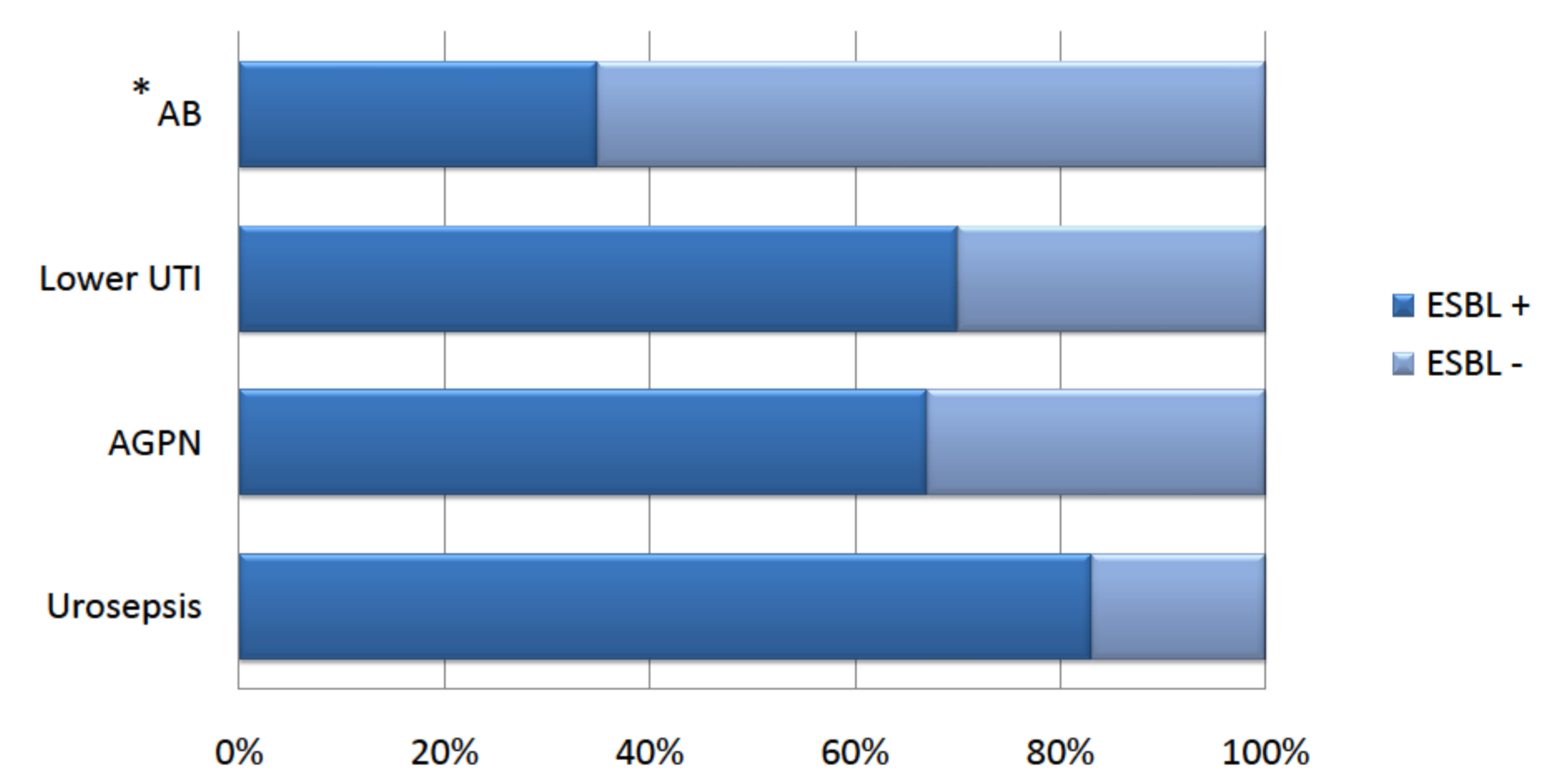
ESBL +
ESBL -

*When patients with history of *Klebsiella spp* upper UTIs (AGPN and urosepsis) were excluded from analysis

Conclusions:

•The incidence of multidrug resistant bacteria significantly increased over past seven years, therefore ESBL (+) strains should be considered when selecting empirical antibiotic therapy for hospitalized RTx presenting with recurrent UTIs and history of prior *Klebsiella* spp infection.

•Upper *Klebsiella* spp UTI were significantly more prevalent in males with urinary flow impairment due to various reasons.