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ORIGINAL ARTICLE

Perioperative antibiotic prophylaxis in renal transplantation: a single-center comparison between two regimens and a brief survey among the Eurotransplant renal transplantation centers

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Abstract

Background Perioperative antibiotic prophylaxis (PAP) is an integral part of kidney transplantation to prevent surgical site infections (SSI). In July 2015, we changed our standard from a multiple-dose to a single-dose (SD) prophylaxis. Here, we report on results with both regimens and a related survey among Eurotransplant renal transplantation centers.

Methods From July 2015, all kidney graft recipients of our center were scheduled to receive SD i.v. cefazolin (group SD, $n=107$). They were compared to patients, transplanted since January 2014, receiving our previous standard (i.v. piperacillin/flucloxacillin) until postoperative day (POD) 7, plus oral sultamicillin until POD 10 (group MD, $n=105$). The primary endpoint was the number of SSIs during a 3-month observational period.

Results The frequency of SSI episodes was generally low (group SD vs. MD: 2 vs. 4, $p=0.40$). Of note, urinary tract infections occurred in 40 SD vs. 36 MD patients, respectively ($p=0.60$). Urinary tract infections were caused by Escherichia coli in 36.8%. Female gender was the only independent risk factor on multivariate analysis ($p=0.002$). In addition, 12 episodes of urosepsis in both groups occurred. All-cause infection with multi-resistant bacteria occurred less frequently in SD vs. MD patients (3.7% vs. 8.6%, $p=0.16$). A majority of Eurotransplant centers used i.v. single-dose cephalosporins (36.9%), although substances and duration varied remarkably.

Conclusion Single-dose cefazolin was equally effective and less expensive compared to our previous MD regimen. Based on these findings, we conclude that future prospective studies should be designed to confirm the non-inferiority of single-dose antibiotic regimens.

Keywords Antibiotic · Prophylaxis · Surgical site infection · Kidney transplantation · Survey

Abbreviations

ABMR	Antibody-mediated rejection
AB0i	AB0-incompatible
DGF	Delayed graft function
EAU	European Association of Urology
ITT	Intention-to-treat
MDR	Multidrug-resistant
MRGN	Multidrug-resistant Gram-negative
NODAT	New onset diabetes after transplantation
PAP	Perioperative antibiotic prophylaxis
POD	Postoperative day
PP	Per-protocol
SSI	Surgical site infection
UTI	Urinary tract infection

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Introduction

Administration of perioperative antibiotic prophylaxis (PAP) to prevent surgical site infections (SSI) complements renal transplantation. In 1988, Cohen et al. [1] showed that PAP with three doses of cefuroxime and piperacillin significantly reduced the rate of wound infections as compared to

patients who received no prophylaxis. Nowadays, guidelines authored by different organizations on the perioperative care of renal transplant recipients exist [2–6]. However, not all of these guidelines include recommendations on the antimicrobial prophylaxis. The existing recommendations are not uniform, and the underlying evidence is weak. According to the current guidelines of the European Association of Urology (EAU), a single-dose regimen is recommended in uncomplicated situations [7]. In a retrospective analysis of 442 renal allograft recipients, who received no PAP except trimethoprim/sulfamethoxazole as *Pneumocystis jirovecii* prophylaxis, Laftavi et al. [8] observed only 9 (2%) SSIs. Based on these findings the authors suggest that PAP should only be used in patients with an increased risk of SSI.

In view of a globally increasing resistance to antibiotics, it is especially important to further optimize PAP in renal transplantation. Based on the recommendation of an internal interdisciplinary committee consisting of urologists, nephrologists and microbiologists, we changed our clinical standard from a 10-day multiple-dose regimen including three different agents (2 g piperacillin i.v. bid plus 2 g flucloxacillin i.v. bid starting immediately before transplantation until postoperative day (POD) 7, plus 375 mg sultamicillin p.o. from POD 8 until POD 10) to a single agent single-dose regimen (2 g cefazolin i.v.) in July 2015. Here, we compare 3 months post transplant clinical outcome of patients treated with either multiple-dose (group MD) or single-dose (group SD) PAP.

Patients and methods

We performed a retrospective analysis of all 212 consecutive renal allograft recipients transplanted between January 2014 and March 2017 at the Charité University Hospital Campus Mitte to investigate the incidence of surgical site infections and other bacterial infections. Relevant demographic data [1, 8], major adverse events, infection episodes and important clinical outcome parameters such as surgical complications, the occurrence of delayed graft function (DGF), renal function, graft survival, patient survival, operation time, the length of hospital stay, and rehospitalisations were recorded. DGF was defined as the need for dialysis treatment within 7 days post transplant. The observation time comprised 3 months.

Between January 2014 and June 2015, all patients (group MD) were scheduled to receive 2 g piperacillin i.v. bid plus 2 g flucloxacillin i.v. bid starting immediately before transplantation until POD 7, plus 375 mg sultamicillin p.o. bid from POD 8 until POD 10, the day of scheduled removal of the urinary catheter. Between July 2015 and March 2017, all patients (group SD) were scheduled to receive 2 g cefazolin i.v. immediately before transplantation, plus 2 g cefazolin i.v. if the operation time exceeded 4 h. In case of relevant preexisting donor or recipient infections, PAP was individually adapted. Patients with known penicillin or cephalosporin allergy received 200 mg ciprofloxacin i.v. bid until POD 7, followed by 250 mg ciprofloxacin p.o. bid from POD 8 until POD 10 (group MD), or a single dose of 400 mg ciprofloxacin i.v. immediately before transplantation (group SD).

At transplantation, complement-dependent cytotoxicity crossmatch was negative in all patients and graft allocation was based on a negative virtual crossmatch by considering current and historical unacceptable antigens as defined by solid-phase assays (ELISA and Luminex).

The operation started after the placement of an internal jugular vein catheter. Recipient skin was prepared using betadine solution. The kidney graft was flushed with a histidine–tryptophan–ketoglutarate solution. Renal transplantation was performed via a pararectal incision using the standard extraperitoneal technique with placement of the graft in the iliac fossa and end-to-side anastomosis between the renal vessels and the external iliac vessels. The kidney graft was placed extraperitoneally with a ureteral implantation according full-thickness technique with two running sutures and insertion of a double-J ureteral stent. In both groups, the removal of the urinary catheter was scheduled for POD 10, and the removal of the ureteral stent was scheduled for 6 weeks post transplant.

At 2 h before transplantation and on POD 4 all patients received 20 mg basiliximab i.v. Standard triple maintenance immunosuppression consisted of tacrolimus (target level 5–10 ng/mL) or cyclosporine A (target level 100–200 ng/mL) in combination with mycophenolate mofetil (2000 mg/day) or enteric-coated mycophenolate sodium (1440 mg/day) and 500 mg methylprednisolone i.v. at the time of transplantation, followed by 250 mg on POD 1, 125 mg on POD 2, and stepwise tapering to 4 mg/day at 3 months. Patients received oral *P. jirovecii* prophylaxis consisting of trimethoprim/sulfamethoxazole (480 mg/day) for 6 months and *Cytomegalovirus* prophylaxis with valganciclovir adapted to renal function for at least 3 months. Additionally, all patients received oral amphotericin B suspension for 8 weeks. Renal biopsies were taken on indication and assessed according to the Banff classification [9]. After discharge, all patients were closely monitored in our outpatient department including wound inspection, duplex ultrasound of the transplant, and complete laboratory investigation. Outpatient visits were scheduled once to twice weekly after discharge to once every 2–3 weeks at 3 months after transplantation. Wound inspection was carried out daily during the inpatient stay immediately after transplantation and at every outpatient visit during the first 6 weeks after transplantation. In case of suspected infections such as unexplained fever/chills and/or urinary symptoms, the respective cultures and diagnostics were initiated.

SSI was defined according to the definition of the Center for Disease Control and Prevention [10]. A diagnosis of SSI was made in patients with clinical signs of SSI in combination with a positive wound swab. Urine cultures were taken upon clinical suspicion of UTI. A diagnosis of UTI was made in patients with clinical signs of UTI in combination with a positive urine culture containing $\geq 10^5$ cfu/mL. Any other examinations for potential infections were carried out in case of a clinical suspicion of infection. Sepsis was defined according to the 2001 International Sepsis Definitions Conference [11].

Multidrug-resistant Gram-negative rods (MRGN) are characterized by their resistance to three (3 MRGN) or all four (4 MRGN) antibiotic lead compounds (Table 5) according to the guidance document from the Robert Koch Institute [12].

In addition, we evaluated current practice in Eurotransplant adult renal transplantation centers using a standardized questionnaire. Centers were contacted via phone call, email or fax. The survey contained questions on (1) whether a standard PAP does exist, (2) whether it is dependent on the transplantation setting, i.e., postmortal transplantation, living donor transplantation, AB0i transplantation, transplantation after desensitization, (3) the antibiotic of choice including dosage and duration, and (4) the alternative antibiotic of choice in case of allergy. Finally, we asked, (5) whether prophylaxis is changed in case of relevant culture results of the donor. The duration of prophylaxis was divided into 4 categories: 'single' = single shot, 'brief' = up to 72 h, 'intermediate' = 4–10 days, 'extended' = more than 10 days. Dosing was described as uniform standard dose or adapted to eGFR.

All patient records including our web-based electronic patient record system 'TBase' [13] were thoroughly reviewed for the relevant parameters. The study was approved by the institutional Ethics Committee (EA1/048/14). Data were analyzed using intention-to-treat (ITT) and per-protocol (PP) analyses. Comparison between groups was carried out by Fisher´s exact test for nominal variables and Mann–Whitney *U* test or *t* test for ordinal and continuous variables, as appropriate. The risk factors for UTI were assessed using a two-step approach. In a first step, we tested differences in all clinical variables (Tables 1, 2, 3) between patients with and without UTI depending on the distribution of the variables by Fisher's exact test, Mann–Whitney *U* test or *t* test. If an association with a *p* value lower than 0.2 was detected, the respective variable was selected for the multivariable analysis. The threshold of 0.2 was chosen, because a lower *p* value may exclude parameters from the analysis that show a significant association in presence of another variable (interaction of two variables). Patient and graft survival were analyzed according to Kaplan–Meier with a log-rank test. A probability of less than 0.05 was considered statistically significant. All *p* values reported are results of two-sided testing. Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

We compared 107 patients, who were scheduled to receive single-dose prophylaxis between July 2015 and March 2017 (group SD), with 105 patients, who were scheduled to receive multiple-dose prophylaxis between January 2014 and June 2015 (group MD). In both groups, several patients did not receive the scheduled treatment (group SD vs. MD: 19.6% vs. 13.3%, $p = 0.27$) (Fig. 1). Therefore, all data were analyzed using ITT and PP analyses, respectively. The main reasons for choosing another antibiotic regimen were allergy ($n = 18$) and preexisting infection of the donor ($n = 12$) or recipient ($n = 3$). In 2 cases, the change of the antibiotic regimen was an individual decision of the physician in charge. The relevant patient characteristics including donor, recipient, operation, immunosuppression, and catheter data are shown in Table 1.

We found no significant differences between both groups except that the operation time was shorter and that the central venous line was removed earlier in group SD. The reason for the former may be an improvement of the individual skills of the operating surgeons, as there were no major changes among the team of surgeons in the respective period of time. The latter was caused by the reduced duration of PAP in group SD. Serum creatinine at 3 months after transplantation was similar in both groups (group SD vs. MD: 1.45 ± 0.48 mg/dL vs. 1.43 ± 0.53 mg/dL, $p = 0.48$). Concerning the underlying renal disease, there were no significant differences between both groups (Table 2). Both groups were also well balanced regarding the relevant risk factors for SSIs such as age, gender, extended criteria donors, diabetes, body mass index, the transplantation procedure itself, immunosuppression and the underlying renal disease.

Adverse events

Major adverse events, which might influence the occurrence of SSIs are depicted in Table 3. The incidence of DGF was similar in both groups (group SD vs. MD: 28.0% vs. 29.5%, $p = 0.88$). In group SD, one patient died because of ventricular rupture following myocardial infarction on POD 13, another patient died following non-traumatic intracerebral bleeding on POD 14. Graft survival including death with a functioning graft was not different between both groups ($p = 0.24$). In group MD, five kidneys failed within 3 months after transplantation because of recurrent nephrotic-range

Table 1 Patient characteristics

	ITT-analysis			PP-analysis		
	Group SD	Group MD	*p* value	Group SD	Group MD	*p* value
Number of all patients	107	105		86	91	
Patients treated according to protocol	86 (80.4%)	91 (86.7%)	0.27			
Donor age	53.5 ± 12.6	52.8 ± 14.1	0.95	53.2 ± 12.7	52.3 ± 14.7	0.85
Female donor	50 (46.7%)	55 (52.4%)	0.49	40 (46.5%)	52 (57.1%)	0.18
Living donor	44 (41.1%)	45 (42.9%)	0.89	38 (44.2%)	42 (46.2%)	0.88
Extended criteria donor	36 (33.6%)	30 (30.4%)	0.46	29 (33.7%)	24 (26.3%)	0.33
Recipient age	50.2 ± 14.2	51.6 ± 13.4	0.54	48.5 ± 14.6	51.3 ± 13.9	0.20
Female recipient	44 (41.1%)	40 (38.1%)	0.68	32 (37.2%)	30 (33.0%)	0.64
Diabetes including NODAT	11 (10.3%)	12 (11.4%)	0.83	7 (8.1%)	8 (8.8%)	1.00
Body mass index	25.1 ± 4.9	25.8 ± 4.8	0.30	25.0 ± 5.1	25.7 ± 4.7	0.29
Waiting time (days)	1835 ± 1521	1718 ± 1542	0.63	1780 ± 1551	1546 ± 1451	0.37
First transplantation	101 (94.4%)	94 (89.5%)	0.18	81 (94.2)	82 (90.1%)	0.30
AB0i transplantation	9 (8.4%)	12 (11.4%)	0.50	9 (10.5%)	12 (13.2%)	0.65
Cold ischemia time (h)	8.7 ± 6.3	8.0 ± 6.0	0.33	8.2 ± 6.2	7.7 ± 6.1	0.55
Operation time (min)	181 ± 43	192 ± 41	0.03	179 ± 45	189 ± 41	0.06
Baseline immunosuppression						
Rituximab (AB0i transplantation)	9 (8.4%)	12 (11.4%)	0.50	9 (10.5%)	12 (13.2%)	0.65
Basiliximab	106 (99.1%)	104 (99.0)	1.00	85 (98.8%)	90 (98.9%)	1.00
Methylprednisolone	107 (100%)	104 (99.0%)	0.50	86 (100%)	90 (98.9%)	1.00
Calcineurin inhibitor	105 (98.1%)	104 (99.0%)	1.00	84 (97.7%)	90 (98.9%)	0.61
Belatacept	2 (1.9%)	0 (0%)	0.50	2 (2.3%)	0 (0%)	0.24
Mycophenolic acid	107 (100%)	104 (99.0%)	0.50	86 (100%)	90 (98.9%)	1.00
Removal of urinary catheter (days)	10.1 ± 1.4	10.2 ± 1.4	0.32	10.1 ± 1.6	10.2 ± 1.3	0.24
Removal of double-J ureteral stent (days)	47.8 ± 17.6	49.9 ± 16.6	0.53	47.3 ± 17.2	50.2 ± 15.9	0.45
Removal of central venous line (days)	6.2 ± 3.0	7.5 ± 2.4	< 0.001	6.3 ± 3.2	7.5 ± 2.4	< 0.001

Rituximab was exclusively administered in patients, who underwent AB0i renal transplantation

AB0i AB0 incompatible, *NODAT* new onset diabetes after transplantation

Table 2 Underlying renal disease

	ITT-analysis			PP-analysis		
	Group SD *n* = 107	Group MD *n* = 105	*p* value	Group SD *n* = 86	Group MD *n* = 91	*p* value
Glomerulopathy	50 (46.7%)	40 (38.1%)	0.21	42 (48.8%)	36 (39.6%)	0.23
ADPKD	15 (14.0%)	25 (23.8%)	0.08	12 (14.0%)	21 (23.1%)	0.13
Reflux/obstruction	8 (7.5%)	3 (2.9%)	0.21	7 (8.1%)	3 (3.3%)	0.20
Interstitial nephritis	8 (7.5%)	7 (6.7%)	1.00	6 (7.0%)	6 (6.6%)	1.00
Arterial hypertension	6 (5.6%)	7 (6.7%)	0.78	3 (3.5%)	6 (6.6%)	0.50
Diabetes mellitus	5 (4.7%)	4 (3.8%)	1.00	4 (4.7%)	4 (4.4%)	1.00
Other	8 (7.5%)	14 (13.3%)	0.18	7 (8.1%)	10 (11.0%)	0.61
Unknown	7 (6.5%)	5 (4.8%)	0.77	5 (5.8%)	5 (5.5%)	1.00

ADPKD autosomal dominant polycystic kidney disease

focal segmental glomerulosclerosis ($n = 2$), acute antibody-mediated rejection (ABMR) ($n = 1$), and severe *Candida albicans* arteritis ($n = 2$). The latter 2 recipients were reported previously in detail [14]. They had received their kidney from the same donor in whom tissue invasive *C. albicans* infection was not known at the time of transplantation. Despite early antifungal treatment including echinocandins, both patients experienced hemorrhagic *C. albicans* arteritis starting on POD 6, necessitating blood transfusions, operative revisions, and finally nephrectomy of the allograft

Table 3 Clinical outcome and adverse events during the early (3 months) post transplant period

	ITT-analysis			PP-analysis		
	Group SD $n=107$	Group MD $n=105$	p value	Group SD $n=86$	Group MD $n=91$	p value
Delayed graft function	30 (28.0%)	31 (29.5%)	0.88	22 (25.6%)	25 (27.5%)	0.87
Patient survival at 3 months	105 (98.1%)	105 (100%)	0.16	84 (97.7%)	91 (100%)	0.15
Graft survival at 3 months	105 (98.1%)	100 (95.2%)	0.24	84 (97.7%)	86 (94.5%)	0.29
Rejection						
Patients	12 (11.2%)	6 (5.7%)	0.22	9 (10.5%)	6 (6.6%)	0.42
Episodes	12	8	0.16	9	8	0.37
Operative revision						
Patients	15 (14.0%)	18 (17.1%)	0.57	13 (15.1%)	15 (16.5%)	0.84
Reason						
Wound dehiscence	9	5	0.41	7	4	0.36
Lymphocele	3	5	0.50	3	5	0.72
Hematoma/bleeding	2	5	0.28	2	4	0.68
Renal vein thrombosis	1	0	1.00	1	0	0.49
Stenosis of the arterial anastomosis	0	1	0.50	0	1	1.00
Arterial kinking	0	1	0.50	0	1	1.00
Ureteral obstruction	0	1	0.50	0	0	1.00
Rehospitalisation						
Patients	41 (38.3%)	48 (45.7%)	0.33	28 (32.6%)	40 (44.0%)	0.13
Events	55	69	0.19	39	58	0.09
Reason						
Infection	17	21	0.31	12	13	0.32
Wound complication	10	6	0.44	6	5	0.68
Cardiovascular	8	8	0.97	7	8	0.88
Lymphocele	6	8	0.50	6	8	0.58
Other	14	26	0.15	8	24	0.03

In group SD, two patients died because of acute cardiovascular events (myocardial infarction and non-traumatic intracerebral bleeding). In group MD, five renal allografts failed because of refractory, nephrotic-range focal segmental glomerulosclerosis ($n=2$), severe hemorrhagic *Candida albicans* arteritis ($n=2$, same donor), and acute antibody-mediated rejection ($n=1$). As events were counted the number displayed is higher than the patient number

to prevent further fatal bleeding events. Both patients survived this severe and potentially life-threatening complication. These 2 cases are not mentioned in Table 4, as they are not bacterial infections.

The frequency of rejection episodes, operative revisions and rehospitalisations were not significantly different between groups (Table 3). The most common reasons for operative revision were wound healing disorders including wound dehiscences ($n=14$), lymphoceles ($n=8$), and hematomas/bleedings ($n=7$) in the two cohorts. The most common causes for rehospitalisation were infections ($n=38$), wound complications ($n=16$), cardiovascular events ($n=16$), and lymphoceles ($n=14$).

Bacterial infection episodes

We recorded all bacterial infections during the first 3 months after transplantation. The frequency of bacterial SSIs was generally low (2.8%) and did not differ between groups (group SD vs. MD: 1.9% vs. 3.8%, $p=0.40$). The mean time to SSI was 24.7 (15–31) days. All SSIs were superficial incisional SSIs. The pathogens isolated from the respective cultures are shown in Table 4. In group MD, two episodes of SSI were caused by multidrug-resistant (MDR) *Escherichia coli* (Table 5), whereas none was caused by MDR organisms in group SD. Three of 6 patients with SSI required operative revision.

By far, the most common post transplant bacterial infection was UTI ($n=76$) including urosepsis ($n=12$) accounting for 83% (88/106) of all bacterial infection episodes in both groups (Table 4). Most UTIs were caused by *E. coli* ($n=31$), followed by *Enterococcus faecalis* ($n=14$) and *Klebsiella species* ($n=11$). UTIs including urosepsis occurred on average 35.5 (1–91) days after transplantation. The majority of UTIs occurred before removal of the double-J ureteral stent (61/88, 69.3%). Detailed results are

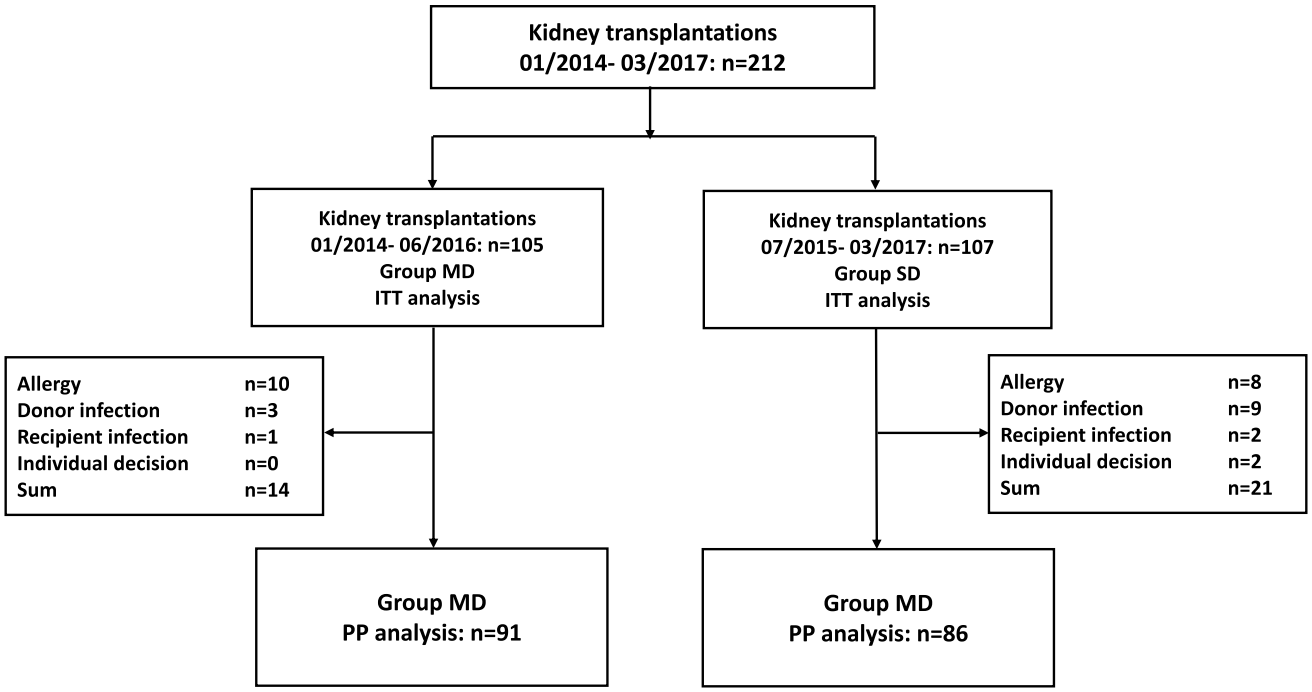

Fig. 1 Flow chart

shown in Table 4. Altogether 15 episodes of UTI including urosepsis were caused by MDR bacteria (Table 5). Generally, there was a trend towards an increased frequency of infections with MDR bacteria in group MD as compared to group SD (Table 5). Using univariate and multivariate analyses, the risk factors for UTI were assessed (Table 6). Female recipient gender turned out to be the only significant risk factor for UTI (OR 3.121, 95% CI 1.509–6.456; $p = 0.002$).

Cost analysis

A detailed cost analysis is provided in Table 7. The change of our PAP to a single-dose regimen reduced the average drug costs per patient by about 380 €, resulting in total cost savings of 32 659 € for 86 patients.

Eurotransplant survey

Current practice in the Eurotransplant area was evaluated using a brief systematic survey among all adult kidney transplant centers. The response rate was 95.6% (65/68 centers responding). We observed a remarkably high variability regarding the applied antibiotics, dosing, and the duration of administration (Table 8, Fig. 2). One center provided no details on the exact dosage. Notably, two centers (3.1%) do not use PAP, whereas 29 (44.6%) centers use 'single shot', 14 (21.5%) 'brief' (≤ 72 h), 14 (21.5%) 'intermediate' (4–10 days), and 6 (9.2%) 'extended' (≥ 10 days) prophylaxis. Thereof, four centers apply trimethoprim/sulfamethoxazole p.o. for 3 or 6 months respectively ('extended') as a combined prophylaxis for SSIs and *P. jirovecii* pneumonia. The overwhelming majority of centers prefer the i.v. administration route (84.6%). More than half of all centers use cephalosporins (60%). In case of allergy or any other contraindication to ß-lactam antibiotics 26 (40.0%) centers use fluoroquinolones, 12 (18.4%) use clindamycin, 4 (6.1%) use carbapenems, 4 (6.1%) use cephalosporins, 2 (3.1%) use dapsone and one center each doxycycline, pentamidine, fosfomycin, trimethoprim/sulfamethoxazole, and one center uses additional vancomycin in case of methicillin-resistant Gram-positive pathogens. Three centers did not administer any prophylaxis in case of any contraindication to ß-lactam antibiotics, and in 4 (6.1%) centers it is an individual decision by the physician in charge. In two centers no details were provided regarding this question.

Discussion

Worldwide, PAP is an integral part of renal transplantation. Unfortunately, the existing recommendations are not consistent and often vague [2–6], and the underlying evidence is weak and partially outdated [1, 15, 16]. Of note, the EAU recommended a single dose prophylactic regimen in their recently published guidelines [7]. Concise guidelines for perioperative antibiotic prophylaxis as well as wound

Table 4 Bacterial infection episodes during the early (3 months) post transplant period

	ITT-analysis			PP-analysis		
	Group SD $n=107$	Group MD $n=105$	p value	Group SD $n=86$	Group MD $n=91$	p value
Patients	36 (33.6%)	43 (41.0%)	0.32	23 (26.7%)	35 (38.5%)	0.11
Episodes	49	57	0.37	33	43	0.17
Length of initial hospital stay (days)	13.6 ± 4.5	15.3 ± 7.9	0.05	13.5 ± 4.5	14.8 ± 7.6	0.19
Time to 1st episode (POD)	31.0 (6–73)	32.5 (1–90)	0.44	27.5 (6–73)	36.5 (1–90)	0.39
Surgical site infection	2	4	0.40	1	3	0.34
Staphylococcus epidermidis	1	0		1	0	
Staphylococcus aureus	1	0		0	0	
Corynebacterium species	1	0		1	0	
Escherichia coli	0	3		0	3	
Pseudomonas aeruginosa	0	2		0	2	
Unknown	0	1		0	0	
Urinary tract infection	40	36	0.60	28	28	0.89
Enterococcus faecalis	6	5		1	4	
Enterococcus faecium	1	2		1	2	
Staphylococcus	1	0		0	0	
Escherichia coli	17	11		12	6	
Klebsiella pneumoniae	6	3		6	2	
Enterobacter cloacae	3	2		3	2	
Proteus mirabilis	2	0		2	0	
Raoultella planticola	0	2		0	2	
Unknown	6	14		4	11	
Sepsis	5	10	0.25	3	6	0.35
Urosepsis	5	7	0.72	3	4	1.00
Enterococcus faecalis	0	3		0	1	
Escherichia coli	2	1		1	1	
Klebsiella oxytoca	0	1		0	0	
Klebsiella pneumoniae	1	0		0	0	
Enterobacter cloacae	1	0		1	0	
Pseudomonas aeruginosa	1	1		1	1	
Proteus vulgaris	0	1		0	1	
Citrobacter freundii	0	1		0	0	
Unknown	0	1		0	0	
Clostridium difficile colitis	1	1	0.99	0	0	1.00
Pneumonia	1	3	0.31	1	3	0.34
Peritoneal catheter infection	0	2	0.15	0	2	0.17
Fever of unknown origin	0	1	0.31	0	1	0.33

Two different bacteria were isolated in 1 episode of group SD and in 2 episodes of group MD. Abbreviations: POD, postoperative day; tx, transplantation

POD postoperative day, *tx* transplantation

infections were listed for the first time in the 2017 edition of the EAU Guidelines on Renal Transplantation reflecting an increasing interest in the topic and a growing body of evidence regarding both, the definition of risk factors as well as the prophylaxis of wound infections. Both aspects were not listed as separate topic in the preceding editions.

To avoid any potential harm to their recipients during the critical early phase after transplantation, some transplant physicians even tend to apply broad-spectrum antibiotics for an extended period of time. Accordingly, our own protocol had remained unchanged for years given the existing low rate of infections. However, in times of increasing antibiotic resistances worldwide with higher rates of MDR, we reviewed our standard procedure in 2015. Following intense discussions among urologists, nephrologists, and microbiologists, we changed our standard prophylaxis. Here, we

Table 5 Infections caused by multidrug-resistant bacteria

	ITT-analysis			PP-analysis		
	Group SD $n=107$	Group MD $n=105$	p value	Group SD $n=86$	Group MD $n=91$	p value
Patients	4 (3.7%)	9 (8.6%)	0.16	3 (3.5%)	7 (7.7%)	0.33
Events	6	11	0.15	5	8	0.24
Surgical site infection						
Patients	0 (0%)	2 (1.9%)	0.24	0 (0%)	2 (2.2%)	0.50
Events	0	2	0.15	0	2	0.17
Escherichia coli 3MRGN[a]	0	2		0	2	
Urinary tract infection including urosepsis						
Patients	4 (3.7%)	7 (6.7%)	0.37	3 (3.5%)	5 (5.5%)	0.72
Events	6	9	0.34	5	6	0.53
Escherichia coli 3MRGN[a]	0	4		0	1	
Escherichia coli ESBL	1	2		1	2	
Klebsiella pneumoniae 3MRGN[a]	5	0		4	0	
Klebsiella pneumoniae 4MRGN[b]	0	1		0	1	
Vancomycin resistant *Enterococcus*	0	2		0	2	

ESBL extended-spectrum ß-lactamase, *MRGN* multi-drug-resistant Gram-negative bacteria

[a]3MRGN: Isolates resistant to 3 out of 4 relevant antimicrobial classes (acylureidopenicilin, third- or fourth-generation cephalosporins, carbapenems, and fluoroquinolones) are classified as 3MRGN

[b]4MRGN: Isolates resistant to all 4 classes are classified as 4MRGN as defined by Robert Koch Institute in Germany, 2012

Table 6 Risk of urinary tract infection during the early (3 months) posttransplant period

	Univariate analysis	OR	Multivariate analysis 95% CI	p value
Living donor	0.17	0.738	0.245–2.222	0.589
Female recipient	< 0.001	3.121	1.509–6.456	0.002
Interstitial nephritis	0.08	2.112	0.579–7.712	0.258
First transplantation	0.05	0.410	0.125–1.350	0.143
Waiting time	0.10	1.009	0.884–1.152	0.892

Univariate and binary logistic regression analysis (inclusion)

OR odds ratio

present a comparison between patients, who were treated with the new single-dose regimen, and patients treated with our previous 10-day multiple-dose regimen. Because of deviations from the scheduled protocols, we applied both ITT and PP analyses.

Both groups were comparable concerning the relevant characteristics. In addition, major adverse events such as rejection episodes, operative revisions and rehospitalisations were also equally distributed. In agreement with the existing literature [8, 15, 17], the overall frequency of SSIs was relatively low (6/212, 2.8%) with no differences between both groups. In a randomized controlled trial published in 2015, one-shot perioperative prophylaxis was also found to be equally effective when compared to multiple dose prophylaxis [18]. In this study, patients at a higher risk for periprocedural complications were excluded (diabetes, repeat transplant, AB0i transplantation), two different antibiotics were used in both groups, the recruitment period was relatively long, and follow-up was restricted to 1 month. In comparison, the recruitment period of our study was substantially shorter, we included all patients, independent of their individual risk, PAP was consistent in each group in

Table 7 Drug cost analysis

	Group SD $n=86$	Group MD $n=91$
Total cost for perioperative antibiotic prophylaxis (€)		
Drug cost per patient	8.05	387.81
Drug cost for all treated patients	692.30	35,290.71
Drug cost savings per patient	379.76	
Drug cost savings for all patients ($n=86$)	32,659.36	

The calculation of drug costs is based on the official German price list of September 2017

Table 8 Perioperative antibiotic prophylaxis in Eurotransplant adult kidney transplant centers

Antibiotic regimen	Centers *n* (%)	Administration (i.v./p.o.)	Dose range	Duration			
				Single	Brief	Intermediate	Extended
None	2 (3.1)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Piperacillin	1 (1.5)	i.v.	4 g q12 h			1	
Ampicillin–sulbactam	8 (12.3)	i.v.	0.5 g q12 h → 3 g q8 h	3	3	2	
Sultamicillin	1 (1.5)	p.o.	0.375 g q12 h				1
Amoxicillin–clavulanic acid	2 (3.1)	i.v.	1.2 g q8 h → 3 g q12 h		1	1	
Piperacillin–tazobactam	4 (6.1)	i.v.	4.5 g q8 h → 4.5 g q12 h	1	1[a]	2	
Cefazolin	15 (23.1)	i.v.	1 g → 2 g	11	3	1	
Cefuroxime	14 (21.5)	i.v.	0.75 g q8 h → 1.5 g q8 h	9	3	2	
Ceftriaxone	9 (13.8)	i.v.	2 g → 4 g	5[b]	1[c]	3	
Cefotaxime	1 (1.5)	i.v.	n.a.		1[d]		
Ertapenem	1 (1.5)	i.v.	1 g q24 h		1		
Imipenem	2 (3.1)	i.v.	0.5 g q12 h/adapted to GFR			2	
Ciprofloxacin	1 (1.5)	i.v.	0.4 g q12 h		1		
Ciprofloxacin	1 (1.5)	p.o.	0.25 g q12 h			1	
Trimethoprim/sulfamethoxazole	4 (6.1)	p.o.	0.96 g/adapted to GFR				4
Fosfomycin plus Sultamicillin	1 (1.5)	p.o.	3 g every 5th day				1[e]
Metronidazole	2 (3.1)	i.v.	0.5 g q12 h	1	1		

Current practice in perioperative antibiotic prophylaxis among Eurotransplant adult kidney transplant centers. Total number of centers: $n = 68$; centers responding to the questionnaire: $n = 65$. Note, percentages refer to the number of responding centers

[a]In combination with ciprofloxacin

[b]In combination with metronidazole

[c]In combination with metronidazole in one center

[d] Dose not provided

[e]Extended Fosfomycin in combination with one dose of sultamicillin adapted to GFR

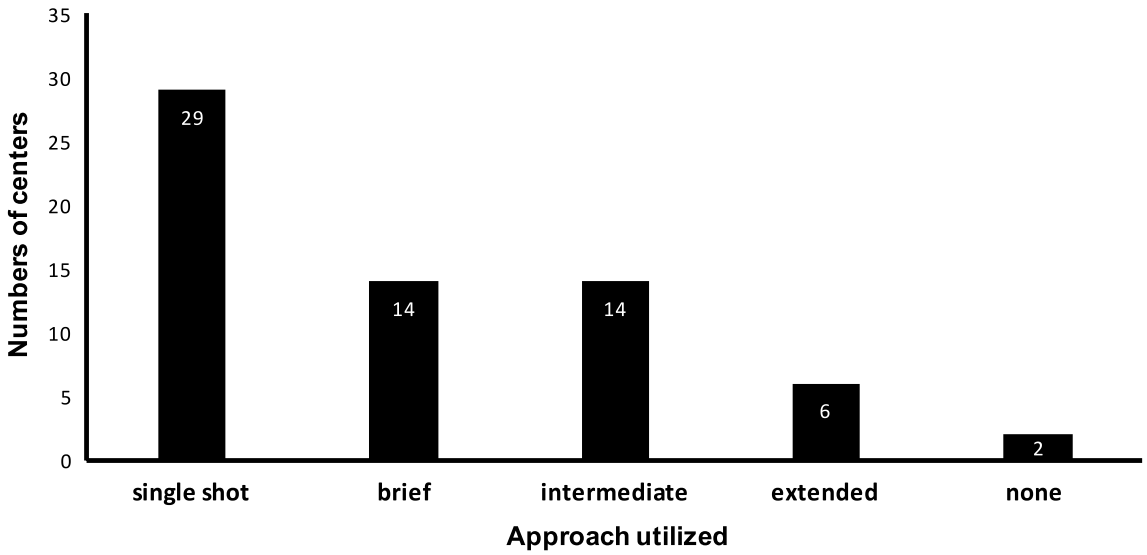

Fig. 2 Antibiotic prophylaxis among kidney transplant centers. Participating adult kidney transplant centers across Eurotransplant and duration of perioperative antibiotic prophylaxis. The duration of prophylaxis was divided into 4 categories: 'single' = single shot, 'brief' = up to 72 h, 'intermediate' = 4–10 days, 'extended' = more than 10 days

the PP-analysis, and the observation period was markedly longer. Therefore, our results indicate that single-dose PAP can be safely extended to virtually all renal transplant recipients independent of their individual risk profile.

In comparison, UTI including urosepsis was relatively frequent and accounted for 83% of all bacterial infection episodes, mainly provoked by *E. coli*. Multivariate logistic regression analysis revealed that female recipient gender was the only significant risk factor for UTI. MDR bacteria such as MRGN, extended-spectrum ß-lactamase (ESBL)-producing bacteria, or vancomycin-resistant enterococci accounted for 16% (17/106) of all bacterial infection episodes. Interestingly, there was a trend towards a higher frequency of infections with MDR bacteria in group MD.

The new PAP regimen did not influence relevant outcome parameters. The death of two patients in group SD was clearly caused by cardiovascular events, which were not related to any infectious event. Importantly, two renal allografts were lost by *C. albicans* arteritis. Both patients had received a kidney from a donor, in whom a diagnosis of tissue-invasive *C. albicans* infection was established after transplantation [14]. Several case reports exist on this important topic, which all highlight that *Candida* arteritis is an extremely dangerous complication following transplantation often leading to graft loss or death [19–22]. Two graft losses were caused by early recurrence of idiopathic nephrotic-range focal segmental glomerulosclerosis. Both cases were refractory to multimodal treatment including steroid boli, high-dose i.v. cyclosporine and plasma exchange [23], as well as rituximab treatment [24]. Both patients returned to maintenance dialysis treatment within 3 months after transplantation (POD 73 and 82). One graft loss was caused by early ABMR and did not respond to treatment with steroids, low-dose IVIG, rituximab and plasma exchange [25].

Current knowledge on the incidence, nature, spectrum of pathogens, and risk factors of SSIs was recently summarized by Anesi et al. [26]. Our survey on the current standard of care in Eurotransplant adult kidney transplant centers revealed a heterogeneous picture concerning the applied substances, the route of administration and the duration of treatment. The majority of centers prefer single shot i.v. application of cephalosporins. Interestingly, the individual range extends from complete avoidance of any PAP (except for routine prophylaxis for *P. jirovecii*), to the application of carbapenems for up to 7 days. Of course, the local spectrum of bacteria must be taken into account, and therefore, prophylaxis should be locally adapted and chosen in consultation with local microbiologists. Based on the existing evidence including our own results, a single-dose regimen seems to be recommendable.

The main limitation of our study is the retrospective design and the fact that we did not use a standardized comorbidity index. Nevertheless, we feel that it is justified to conclude that single-shot PAP with cefazolin proved to be equally effective and much more cost-effective as compared to our previous 10-day multiple-dose prophylaxis. Notably, the new regimen generated substantial cost savings of more than 30.000 €. The observed rate of SSIs was generally very low, although we did not exclude patients with potential risk factors. The most common bacterial infections were UTIs, most frequently caused by *E. coli* and sometimes leading to urosepsis. The fact that the frequency of infections caused by MDR bacteria tended to be higher in those patients, who had received multiple-dose prophylaxis, indicates that a reduction of the extent of the prophylaxis may help to reduce the number of MDR infections. In future, prospective randomized studies on PAP in renal transplantation are necessary, in which patients are stratified according to relevant comorbidities and risk factors including immunosuppression. These studies should be multicentric and international, to consider site-specific differences regarding the spectrum of pathogens and the spectrum of antibiotic resistance in different regions or countries. Endpoints of these studies should be the incidence of all kinds of early posttransplant bacterial infections as well as the occurrence of infections with multiresistant bacteria in the later posttransplant period, as a potential consequence of excessive antibiotic prophylaxis. These studies should be designed to confirm the non-inferiority of single-dose antibiotic regimens, to provide the evidence base for future Guideline recommendations.

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