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Article type : Original Article

Impact of different urinary tract infection phenotypes within the first year post-transplant on renal allograft outcomes

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Abstract word count: 200

Word count including abstract: 3452

Tables: 4

Figures: 4

Abbreviations

BKV	BK virus
CFU	Colony Forming Units
CMV	Cytomegalovirus
eGFR	Estimated Glomerular Filtration Rate
STCS	Swiss Transplant Cohort Study
UTI	Urinary Tract Infection

Abstract

In this study we investigated the clinical impact of different urinary tract infection (UTI) phenotypes occurring within the first year after renal transplantation. The population included 2368 transplantations having 2363 UTI events. Patients were categorized into four groups based on their compiled UTI events observed within the first year after transplantation: (i) no colonization or UTI [n=1404; 59%], (ii) colonization only [n=353; 15%], (iii) occasional UTI with 1-2 episodes [n=456; 19%], and (iv) recurrent UTI with ≥3 episodes [n=155; 7%]. One-year mortality and graft loss rate were not different among the four groups, but patients with recurrent UTI had a 7-10ml/min lower eGFR at one year (44ml/min vs 54, 53 and 51ml/min; p<0.001). UTI phenotypes had no impact on long-term patient survival (p=0.33). However, patients with recurrent UTI demonstrated a 10% lower long-term death-censored allograft survival (p<0.001). Furthermore, recurrent UTI was a strong and independent risk factor for reduced death-censored allograft survival in a multivariable analysis (HR 4.41, 95% CI 2.53-7.68, p<0.001). We conclude that colonization and occasional UTI have no impact on pertinent outcomes, but recurrent UTI are associated with lower one-year eGFR and lower long-term death-censored allograft survival. Better strategies to prevent and treat recurrent UTI are needed.

1. Introduction

Urinary tract infection (UTI) is the most frequent infection after renal transplantation and the highest incidence is observed within the first year post-transplant (1,2). The prevalence of UTI varies greatly depending on the study, the population studied, the use of antimicrobial prophylaxis and the length of the follow-up, ranging from 7% to 80% with larger studies reporting one-year incidence around 30% (3–6).

Although UTI in renal transplantation has been studied extensively, many issues are still incompletely understood due to conflicting results in previous studies (6). One important question is whether the occurrence of UTI impairs allograft function. While some studies showed a negative impact (7,8), other investigators reported no difference in graft function between patient cohorts with and without UTI (9,10). Another not yet conclusively clarified issue is whether the occurrence of UTI is associated with a lower patient and allograft survival. Some studies showed a negative impact on both, patient and graft survival (5,11), while other investigators found only a negative impact on allograft survival (12) or no association between UTI and patient or allograft survival at all (13,14). These divergent results might be related to individual limitations in these studies such as low number of included patients, short follow-up time, as well as different definitions and incomplete inclusion of UTI phenotypes.

Additionally, in the past, episodes of asymptomatic bacteriuria/colonization were considered as risk factors for the development of symptomatic UTI and were often treated, although there was little evidence to support this approach (15–17). Indeed, two recent randomized controlled trials demonstrated that treatment of asymptomatic bacteriuria is not beneficial (18,19). However, several larger studies investigating the clinical relevance of UTI have either not distinguished between asymptomatic bacteriuria/colonization and symptomatic UTI or have not included asymptomatic bacteriuria/colonization as an independent UTI phenotype (5,9,11,20,21).

To increase the knowledge regarding the described gaps in the literature, we investigated the impact of different UTI phenotypes (i.e. [i] no UTI or colonization, [ii] colonization(s) only, [iii]

occasional UTI and [iv] recurrent UTI) within the first year after renal transplantation on allograft function, as well as long-term allograft and patient survival in a large, contemporary national cohort.

2. Materials and Methods

2.1. Study design and patient population

The STCS is a multi-center observational long-term follow-up cohort including all solid organ transplant recipients from the six Swiss transplant centers. Details on design and methodology of the STCS have been published elsewhere (22). In the period from May 2008 to December 2017, 2874 kidney transplantations were performed in Switzerland. Five hundred and six of 2874 (18%) transplantations were excluded for the following reasons: no informed consent (n=217), multi-organ transplants (n=158), pediatric recipients (n=90), missing pre-transplant donor-specific HLA antibody assignment (n=28), missing baseline data (n=10), no complete one-year follow-up (n=3). Therefore, the final population consisted of 2368 adult kidney-only transplantations with complete datasets and at least one year of follow-up. The study was approved by the ethics committee of Northwestern and Central Switzerland (www.eknz.ch; project ID 2021-00360).

2.2. Definitions and grouping of UTI events

Urine cultures were taken at all six transplant centers in case of leukocyturia and/or symptoms referring to a UTI. Additionally, at one center, urine cultures were taken at each consultation during the first 6 months after transplantation. All UTI events were classified by an infectious disease specialist and/or nephrologist based on microbiological cultures, urine analyses and recorded clinical symptoms as follows:

(i) Urinary colonization was defined as presence of bacteria and/or fungi in the urine with $\geq 10^5$ CFU/ml in the absence of local and systemic signs or symptoms of infection. This can be regarded as equivalent to 'asymptomatic bacteriuria/UTI'.

(ii) UTI was defined as presence of bacteria and/or fungi in the urine with $\geq 10^5$ CFU/ml in the presence of local and/or systemic signs or symptoms of infection. No distinction between lower UTI (i.e. cystitis) and upper UTI (i.e. pyelonephritis) was recorded in the STCS database.

(iii) Urosepsis was defined as detection of the same pathogen in urine and blood cultures in the presence of local and/or systemic symptoms of infection.

Based on all recorded UTI events within the first year post-transplant, the recipients were categorized into four groups:

(i) no colonization or UTI

(ii) colonization only

(iii) occasional UTI (1-2 UTI episodes)

(iv) recurrent UTI (≥3 UTI episodes)

2.3. Catheter policy and infection prophylaxis

At all six kidney transplant centers, the allograft recipients received a Foley catheter after transplantation, which was removed between postoperative day 4 and 7. A double J-stent was inserted during transplantation as a standard procedure in 5/6 transplant centers, which was removed between two and eight weeks after transplantation. At all centers, patients received trimethoprim-sulfamethoxazole (TMP/SMX) as pneumocystis prophylaxis for 6 months after transplantation. Additionally, at one transplant center, the patients received antibiotic prophylaxis with either amoxicillin/clavulanic acid or ciprofloxacin until the double J-stent was removed.

2.4. Treatment of UTI

UTIs were routinely treated, while colonizations were treated only in 2/6 centers early after transplantation (for the first six months after transplantation and as long as the double J-stent was in situ, respectively). At all centers, patients with recurrent UTI underwent thorough clinical work-up for underlying gynecological or urogenital pathologies.

2.5. Diagnosis of rejection and screening for CMV as well as BKV

Rejection episodes were graded according to the Banff 2013/2015 classification, excluding the 'borderline changes' category (23) . Screening for CMV and BKV replication was performed in all centers according to local practice.

2.6. Outcomes

The investigated outcomes were graft function (i.e. estimated glomerular filtration rate [eGFR] according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24)) at one-year post-transplant, as well as short- and long-term patient and death-censored allograft survival.

2.7. Statistical analysis

JMP software version 16.1 (SAS Institute Inc., Cary, NC) was used for statistical analysis. Categorical data are presented as counts and/or percentages and were analyzed by chi-square test or Fisher's exact test as appropriate. Continuous data are shown as median and interquartile ranges [IQR] and compared by Wilcoxon rank sum tests. For all tests, a (two-tailed) p-value <0.05 was considered to indicate statistical significance. To investigate the impact of UTI phenotypes observed within the first year post-transplant on long-term outcomes, only functioning transplants at one year were included. Time-to-event analyses were performed by the Kaplan-Meier method and compared by the log-rank test. A multivariable Cox regression model was used to investigate independent risk factors for death-censored graft survival beyond the first-year post-transplant.

3. Results

3.1. Incidence of infection events and infection phenotypes

Overall 2363 UTI events were recorded in 2368 transplantations. Colonizations and UTI each accounted for 47% of all events, urosepsis was observed in 6%. While only about a quarter of all colonization were treated with antibiotics, almost all UTI and urosepsis events were managed with antibiotics (***Figure 1A***). In the first month post-transplant, colonization was the most frequent clinical presentation. From post-transplant month two to twelve, the relative proportion of colonization (~45%), UTI (~50%) and urosepsis (~5%) remained very stable (***Figure 1B***).

The one-year incidence of colonization was significantly higher in females compared to males (38% vs 23%; p<0.001). The same observation was made for UTI (40% vs 19%; p<0.001),

but the incidence of urosepsis was similar between females and males (4.4% vs 4.7%; p=0.71) (***Figure 1C***).

Based on all recorded UTI events within the first year post-transplant, 1404/2368 (59%) patients had no colonization or UTI, 353/2368 (15%) had only colonization(s), 456/2368 (19%) had occasional UTI, and 155/2368 (7%) had recurrent UTI (***Figure 1D***).

3.2. Pathogens

During the 2363 UTI events, a total of 2751 pathogens were detected. Bacteria accounted for the vast majority of detected pathogens, while fungi were cultured only in 56/2751 (2%) cases. We observed a different pathogen profile in colonization(s) compared to UTI and urosepsis. This was driven by a higher proportion of *Enterococcus sp.* and *coagulase-negative staphylococci* in colonization(s). The pathogen profile in UTI and urosepsis was very similar with a dominance of *E.coli*, *Enterococcus sp.*, and *Klebsiella sp.* accounting for about 85% of all pathogens (***Figure 2A***).

Interestingly, the pathogen profiles in colonization(s), UTI, and urosepsis remained very stable within the first year post-transplant and did not significantly change from before/after removal of the double J-stent as well as before/after stop of prophylaxis with TMP/SMX (***Figure 2B***).

More than one pathogen was detected in 360/2363 (15.2%) UTI events, with two pathogens detected in the vast majority (two pathogens: n=336; three pathogens: n=20; four pathogens: n=4). The frequency of more than one pathogen detected per UTI event was higher in colonization (232/1111; 20.9%) than in UTI (117/1121; 10.4%) and urosepsis (11/131; 8.4%) (p<0.001). For episodes with two pathogens, the most frequent combinations were *E. coli* plus *Enterococcus sp.* (with 22%, 27% and 55% for colonization, UTI and urosepsis), *E. coli* plus *Klebsiella sp.* (with 12%, 19% and 27% for colonization, UTI and urosepsis) and *Klebsiella sp.* plus *Enterococcus sp.* (with 9%, 12% and 9% for colonization, UTI and urosepsis).

3.2. Baseline characteristics of patient groups

Table 1 summarizes baseline characteristics of patients grouped according to the UTI events within the first-year post-transplant. Recipients with occasional and recurrent UTI were older, more often female, were more likely to have ADPKD, diabetic nephropathy or

reflux/pyelonephritis as primary renal disease, and received more often a kidney from a deceased donor. However, there were no significant differences regarding immunological parameters, as well as induction therapy and maintenance immunosuppression.

3.4. One-year outcomes

Overall, graft loss occurred in 74/2638 (3.1%) cases and death in 49/2368 (2.1%) patients. There were no differences regarding graft loss or death among the four groups. However, patients in the recurrent UTI group had 7-10ml/min lower eGFR than the other groups ($p<0.001$). In addition, the recurrent UTI group had a higher proportion of patient with an eGFR<25 ml/min ($p<0.001$). The number, phenotype and severity of rejection episodes was not different among the four groups (***Table 2***).

3.5. Impact of infection phenotype on long-term patient and graft survival

To investigate the long-term impact of the UTI phenotype observed within the first-year post-transplant, we studied 2245 patients having a functioning allograft at one-year post-transplant. These patients were followed for a median of 4.9 years (2.8-7.1 years). A total of 196 deaths were observed after the first year post-transplant. Overall patient survival was not different among the four UTI groups ($p=0.33$). Stratified by sex, the same observation was made in females ($p=0.32$), while in males there were differences between the four UTI groups–($p=0.006$) with lower survival in males with occasional and recurrent UTI compared to males without colonizations or UTI (***Figure 3A***).

Death-censored allograft survival in the whole cohort was around 10% lower in the recurrent UTI group compared to the other groups ($p<0.001$). Stratified by sex, we made the same observation in females and males ($p<0.001$ and $p<0.001$, respectively). In addition, in males even occasional UTI showed a lower death-censored allograft survival compared to the 'no colonization or UTI' group ($p=0.02$) (***Figure 3B***).

Next, we investigated the impact of UTI phenotypes on death-censored allograft survival in a multivariable Cox proportional hazards model. One hundred and thirty death-censored allograft failures were observed in the cohort of 2245 patients with a functioning allograft at one-year post-transplant. Of these, 61, 15, 29 and 25 events were observed in the no colonization or

UTI, the colonization only, the occasional UTI and recurrent UTI group, respectively. To minimize statistical problems related to overfitting the model, only 14 variables considered as proven or potential risk factors were included. Recurrent UTI was a strong and independent risk factor with a hazard ratio of 4.41 (95% CI 2.53-7.68; p<0.001). Other significant risk factors were male sex (HR 2.21; p<0.001), donor age (HR 1.47 per decade; p<0.001), deceased donor status (HR 1.93; p=0.001), pre-transplant HLA-DSA (HR 1.73; p=0.01), and rejection within the first year (HR for one rejection 1.88 [p=0.01], HR for ≥2 rejections 3.00 [p<0.001]). Neither the occurrence of urosepsis within the first-year post-transplant, nor the primary renal disease were independent risk factors (***Table 3***).

3.6. Comparison between patients with occasional and recurrent UTI

Patients with recurrent UTI had more frequently colonizations and urosepsis than patients with occasional UTI. Other parameters including primary renal disease, sex, age, donor type, transplant center, induction therapy as well as maintenance immunosuppression were not different between the two groups (***Table 4***). The profile of detected pathogens was very similar between the two groups. However, we observed a numerically higher proportion of *Klebsiella sp.* in the recurrent UTI group across all three UTI phenotypes (***Figure 4***).

4. Discussion

The key observations in this study were that (i) colonizations and occasional UTI are not associated with inferior outcomes, and (ii) recurrent UTI are a strong and independent risk for lower eGFR at one year and lower long-term death-censored allograft survival.

These observations are consistent with studies showing that recurrent UTI in renal transplant recipients are associated with an increased risk for development of renal allograft fibrosis (25,26). We hypothesize, that repeated, probably also persisting infection-related injuries might

exhaust the regenerative capacity of the allograft and induce irreversible fibrosis. Intriguingly, the occurrence of urosepsis as a model of a single severe UTI episode was not an independent risk factor for poorer death-censored graft survival in the multivariable analysis, suggesting that the allograft can fully recover, if a single UTI event resolves. However, in this study we did not perform surveillance biopsies that could confirm the postulated mechanism of graft damage due to fibrosis. Interestingly, a recently published study showed that death-censored graft failure often has multifactorial causes, with medical events (including infections) being the most common cause with 36.3% (27).

Britt et al. reported in a study of similar population size that recurrent UTI were not only associated with inferior graft survival, but also reduced patient survival compared to patients with occasional or no UTI (20). In our study, we observed no significant differences in patient survival among the four UTI phenotypes when analyzing the whole cohort. There are several potential explanations for this discrepancy. First, in our study we investigated only recurrent UTI in the first year after transplantation, whereas Britt et al. included the whole post-transplant observation period to classify patients. It might be possible that late recurrent UTI are associated with a higher mortality. Other factors explaining the observed difference in patient survival might be local differences in demographics, comorbidities, antibiotic resistance profiles and access to health care.

Interestingly, only males had significant differences in patient survival among the four UTI phenotypes. In addition, even occasional UTI were associated with a lower death-censored allograft survival in males. This suggests that UTI has a more pronounced clinical impact in males compared to females. Indeed, even occasional UTI in males might be indicative of a more severe underlying problem (e.g. prostatitis), whereas UTI in females are more likely to have a benign course. Notably, although females had a significantly higher frequency of UTI, we observed no differences in the incidence of urosepsis between females and males, suggesting that males are at higher risk for transition from UTI to urosepsis.

In the multivariable Cox regression analysis recurrent UTI were a very strong and independent risk factor for death-censored graft loss, having a hazard ratio similar to recurrent rejection (i.e. ≥2 rejection episodes within the first year post-transplant). Therefore, treatment and prevention of recurrent UTI is important. Unfortunately, this is very challenging, because risk factors for recurrent UTI such as female gender, increased age, deceased donor status, diabetes mellitus, and vesicourethral reflux are not well established (25,28–30). In addition, many proposed risk factors are either not modifiable or difficult to correct. In our analysis, only the occurrence of urosepsis, the frequency of colonizations, and a slightly higher proportion of *Klebsiella sp.* as causative bacteria were associated with recurrent UTI. This suggests that local immunity in the urinary tract and new or pre-transplant unrecognized urological/gynecological problems play a major role for the development of recurrent UTI. To address this question, in-depth analysis of patients with recurrent UTI including the response to various interventions might be very informative.

The most common pathogens observed were *E. coli*, *Enterococcus sp.*, and *Klebsiella sp.* accounting for 66% of colonization, 83% of UTI, and 85% of urosepsis, respectively. We noticed a higher proportion of gram positive bacteria in colonization, while the pathogen profile was very similar in UTI and urosepsis. The distribution of causative pathogens in UTI does not differ relevantly from other studies (31). However, some investigators reported a particularly high rate of colonization or infection with *Enterococcus sp.* in the first month after transplantation. This finding was attributed on the one hand to a positive selection of gram-positive bacteria in the context of perioperative antibiotic therapy, and on the other hand to a colonization of the double J-stent by *Enterococcus sp.* (32,33). Interestingly, the temporal distribution of the causative microorganisms remained relatively stable within the first year post-transplant in our study, even after stopping TMP/SMX prophylaxis and removal of the double J-stent. This suggests that both, TMP/SMX prophylaxis and double J-stent placement, do not significantly alter the microbial profile.

Two or more pathogens were recorded in 20.9% of all colonizations as well as in around 10% of UTI or urosepsis episodes. Recent studies in non-transplant patients reported rates of

polymicrobial UTIs between 4 and 10%, which is slightly lower than in our kidney transplant cohort (34–36). Most of the polymicrobial UTI events in our study were related to co-infection with common UTI-causing bacteria such as *E. coli*, *Enterococcus sp.*, and *Klebsiella sp.* Although we believe that the majority of these episodes occurred due to real co-colonization or co-infection, we cannot exclude the possibility that a certain proportion are due to contamination. Although uro-genital/uro-intestinal fistula might also be a potential explanation for this observation, we regard this a very unlikely.

The strength of this study are the multicenter design with prospective data collection, the size of the investigated population, the inclusion of all UTI phenotypes, and the long follow-up time. Previous studies on the clinical impact of UTI were either smaller, had less granular data, did not include all UTI phenotypes, did not corrected for relevant confounders, or did not have such a long follow-up. Therefore, we believe that this study provides novel and robust information on this highly relevant topic in the current era of immunosuppression.

Our study has also some limitations. First, we could not take into account the severity of UTI (e.g. cystitis vs. acute allograft pyelonephritis), as the STCS does not contain any data in this regard. We assume that this additional granularity of the UTI phenotypes would not have significantly changed the overall conclusion, because the occurrence of urosepsis, representative of a more severe UTI, was not an independent risk factor for impaired death-censored graft survival. Second, we only assessed UTI episodes within the first year. We have chosen to do so, because most UTI episodes occur in this time frame. In addition, we could classify patients according to first-year UTI events and investigate the impact of different UTI phenotypes on subsequent outcomes in a clean way. Third, although this is a national multicenter study, the results might not be transferable to countries with different health care systems, non-Caucasian ethnicities and populations/transplant centers with a lower rate of polymicrobial UTI.

In conclusion, colonizations and occasional UTI have no negative impact on patient and allograft survival. By contrast, recurrent UTI - affecting 7% of all renal allograft recipients - are associated with a lower eGFR at one year and a lower long-term death-censored allograft survival.

Therefore, there is an urgent need to improve treatment strategies and preventive measures for recurrent UTI.

Acknowledgements

This study has been conducted in the framework of the Swiss Transplant Cohort Study, supported by the Swiss National Science Foundation and the Swiss University Hospitals (G15) and transplant centers. The members of the Swiss Transplant Cohort Study are: Patrizia Amico, Andres Axel, John-David Aubert, Vanessa Banz, Beckmann Sonja, Guido Beldi , Christoph Berger, Ekaterine Berishvili, Isabelle Binet, Pierre-Yves Bochud, Sanda Branca, Heiner Bucher, Thierry Carrel, Emmanuelle Catana, Yves Chalandon, Sabina De Geest, Olivier De Rougemont, Sophie De Seigneux, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Nicola Franscini, Christian Garzoni, Paola Gasche Soccal, Christophe Gaudet, Déla Golshayan, Nicolas Goossens, Karine Hadaya, Jörg Halter, Dominik Heim, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Michael Koller (Head of the data center), Mirjam Laager, Bettina Laesser, Roger Lehmann, Alexander Leichtle, Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Michele Martinelli, Valérie McLin, Katell Mellac, Aurélia Merçay, Karin Mettler, Nicolas Mueller (Chairman Scientific Committee), Antonia Müller, Ulrike Müller-Arndt, Beat Müllhaupt, Mirjam Nägeli, Graziano Oldani, Manuel Pascual (Executive office), Klara Posfay-Barbe, Juliane Rick , Anne Rosselet, Simona Rossi, Silvia Rothlin, Frank Ruschitzka, Thomas Schachtner, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Macé Schuurmans, Thierry Sengstag, Federico Simonetta, Susanne Stampf, Jürg Steiger (Head, Excecutive office), Guido Stirniman, Ueli Stürzinger, Christian Van Delden (Executive office), Jean-Pierre Venetz, Jean Villard, Julien Vionnet, Madeleine Wick (STCS coordinator), Markus Wilhlem, Patrick Yerly.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, et al. Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. Clin Infect Dis 2020; 71 (7): e159-e169.
2. Jackson KR, Motter JD, Bae S, Kernodle A, Long JJ, Werbel W, et al. Characterizing the landscape and impact of infections following kidney transplantation. Am J Transplant 2021; 21 (1): 198–207.
3. Müller V, Becker G, Delfs M, Albrecht KH, Philipp T, Heemann U. Do urinary tract infections trigger chronic kidney transplant rejection in man? J Urol 1998; 159 (6): 1826–1829.
4. Karakayali H, Emiroğlu R, Arslan G, Bilgin N, Haberal M. Major infectious complications after kidney transplantation. Transplant Proc 2001; 33 (1-2): 1816–1817.
5. Naik AS, Dharnidharka VR, Schnitzler MA, Brennan DC, Segev DL, Axelrod D, et al. Clinical and economic consequences of first-year urinary tract infections, sepsis, and pneumonia in contemporary kidney transplantation practice. Transpl Int 2016; 29 (2): 241–252.
6. Hollyer I, Ison MG. The challenge of urinary tract infections in renal transplant recipients. Transpl Infect Dis 2018; 20 (2): e12828.
7. Lim J-H, Cho J-H, Lee J-H, Park Y-J, Jin S, Park G-Y, et al. Risk factors for recurrent urinary tract infection in kidney transplant recipients. Transplant Proc 2013; 45 (4): 1584–1589.
8. Ooms L, IJzermans J, Voor In 't Holt A, Betjes M, Vos M, Terkivatan T. Urinary Tract Infections After Kidney Transplantation: A Risk Factor Analysis of 417 Patients. Ann Transplant 2017; 22: 402–408.
9. Camargo LF, Esteves ABA, Ulisses LRS, Rivelli GG, Mazzali M. Urinary tract infection in renal transplant recipients: incidence, risk factors, and impact on graft function. Transplant Proc 2014; 46 (6): 1757–1759.
10. Papasotiriou M, Savvidaki E, Kalliakmani P, Papachristou E, Marangos M, Fokaefs E, et al. Predisposing factors to the development of urinary tract infections in renal transplant recipients and the impact on the long-term graft function. Ren Fail 2011; 33 (4): 405–410.
11. Abbott KC, Swanson SJ, Richter ER, Bohen EM, Agodoa LY, Peters TG, et al. Late urinary tract infection after renal transplantation in the United States. Am J Kidney Dis 2004; 44 (2): 353–362.
12. Giral M, Pascuariello G, Karam G, Hourmant M, Cantarovich D, Dantal J, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. Kidney Int 2002; 61 (5): 1880–1886.
13. Adamska Z, Karczewski M, Cichańska L, Więckowska B, Małkiewicz T, Mahadea D, et al. Bacterial Infections in Renal Transplant Recipients. Transplant Proc 2015; 47 (6): 1808–1812.

14. Pellé G, Vimont S, Levy PP, Hertig A, Ouali N, Chassin C, et al. Acute pyelonephritis represents a risk factor impairing long-term kidney graft function. Am J Transplant 2007; 7 (4): 899–907.
15. Coussement J, Abramowicz D. Should we treat asymptomatic bacteriuria after renal transplantation? Nephrol Dial Transplant 2014; 29 (2): 260–262.
16. Coussement J, Scemla A, Abramowicz D, Nagler EV, Webster AC. Antibiotics for asymptomatic bacteriuria in kidney transplant recipients. Cochrane Database Syst Rev 2018; 2: CD011357.
17. Fiorante S, López-Medrano F, Lizasoain M, Lalueza A, Juan RS, Andrés A, et al. Systematic screening and treatment of asymptomatic bacteriuria in renal transplant recipients. Kidney Int 2010; 78 (8): 774–781.
18. Origüen J, López-Medrano F, Fernández-Ruiz M, Polanco N, Gutiérrez E, González E, et al. Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial. Am J Transplant 2016; 16 (10): 2943–2953.
19. Coussement J, Kamar N, Matignon M, Weekers L, Scemla A, Giral M, et al. Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial. Clin Microbiol Infect 2021; 27 (3): 398–405.
20. Britt NS, Hagopian JC, Brennan DC, Pottebaum AA, Santos CAQ, Gharabagi A, et al. Effects of recurrent urinary tract infections on graft and patient outcomes after kidney transplantation. Nephrol Dial Transplant 2017; 32 (10): 1758–1766.
21. Ariza-Heredia EJ, Beam EN, Lesnick TG, Cosio FG, Kremers WK, Razonable RR. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant 2014; 28 (6): 683–690.
22. Koller MT, van Delden C, Müller NJ, Baumann P, Lovis C, Marti H-P, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. Eur J Epidemiol 2013; 28 (4): 347–355.
23. Loupy A, Haas M, Solez K, Racusen L, Glotz D, Seron D, et al. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. Am J Transplant 2017; 17 (1): 28–41.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150 (9): 604–612.
25. Dupont PJ, Psimenou E, Lord R, Buscombe JR, Hilson AJ, Sweny P. Late recurrent urinary tract infections may produce renal allograft scarring even in the absence of symptoms or vesicoureteric reflux. Transplantation 2007; 84 (3): 351–355.
26. Boor P, Floege J. Renal allograft fibrosis: biology and therapeutic targets. Am J Transplant 2015; 15 (4): 863–886.

27. Mayrdorfer M, Liefeldt L, Wu K, Rudolph B, Zhang Q, Friedersdorff F, et al. Exploring the Complexity of Death-Censored Kidney Allograft Failure. J Am Soc Nephrol 2021; 32 (6): 1513–1526.
28. Alangaden GJ, Thyagarajan R, Gruber SA, Morawski K, Garnick J, El-Amm JM, et al. Infectious complications after kidney transplantation: current epidemiology and associated risk factors. Clin Transplant 2006; 20 (4): 401–409.
29. Song JC, Hwang HS, Yoon HE, Kim JC, Choi BS, Kim YS, et al. Endoscopic subureteral polydimethylsiloxane injection and prevention of recurrent acute graft pyelonephritis. Nephron Clin Pract 2011; 117 (4): c385-9.
30. Mitra S, Alangaden GJ. Recurrent urinary tract infections in kidney transplant recipients. Curr Infect Dis Rep 2011; 13 (6): 579–587.
31. Ariza-Heredia EJ, Beam EN, Lesnick TG, Kremers WK, Cosio FG, Razonable RR. Urinary tract infections in kidney transplant recipients: role of gender, urologic abnormalities, and antimicrobial prophylaxis. Ann Transplant 2013; 18: 195–204.
32. Gołębiewska JE, Dębska-Ślizień A, Rutkowski B. Urinary tract infections during the first year after renal transplantation: one center's experience and a review of the literature. Clin Transplant 2014; 28 (11): 1263–1270.
33. Bonkat G, Rieken M, Siegel FP, Frei R, Steiger J, Gröschl I, et al. Microbial ureteral stent colonization in renal transplant recipients: frequency and influence on the short-time functional outcome. Transpl Infect Dis 2012; 14 (1): 57–63.
34. Arakawa S, Kawahara K, Kawahara M, Yasuda M, Fujimoto G, Sato A, et al. The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection. J Infect Chemother 2019; 25 (2): 104–110.
35. Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2018; 18 (12): 1319–1328.
36. Wojno KJ, Baunoch D, Luke N, Opel M, Korman H, Kelly C, et al. Multiplex PCR Based Urinary Tract Infection (UTI) Analysis Compared to Traditional Urine Culture in Identifying Significant Pathogens in Symptomatic Patients. Urology 2020; 136: 119–126.

Tables

Table 1. Baseline characteristics of patients grouped according to UTI phenotype in the first-year post-transplant.

Parameter	No colonization or UTI (n=1404)	Colonization only (n=353)	1-2 UTI (n=456)	≥3 UTI (n=155)	p-value
Recipient age	54 (43-62)	54 (44-63)	57 (46-65)	58 (47-65)	**<0.001**
Female sex	384 (27%)	136 (39%)	237 (52%)	91 (59%)	**<0.001**
Recipient renal disease					
- ADPKD	251 (18%)	69 (20%)	103 (23%)	33 (21%)	
- Diabetic Nephropathy	108 (8%)	28 (8%)	46 (10%)	15 (10%)	**<0.001**
- Reflux/Pyelonephritis	47 (3%)	24 (7%)	33 (7%)	16 (10%)	
- Other	998 (71%)	232 (65%)	274 (60%)	91 (59%)	
RRT prior to transplantation					
- HD	966 (69%)	252 (71%)	318 (70%)	111 (71%)	0.24
- PD	187 (13%)	48 (14%)	53 (12%)	26 (17%)	
- none	251 (18%)	51 (15%)	84 (18%)	18 (12%)	
Donor age	54 (45-63)	54 (45-62)	56 (43-65)	54 (45-64)	0.75
Deceased donor	827 (59%)	190 (54%)	290 (64%)	105 (68%)	**0.006**
Cold ischemia time [h]	9.2 (7.0-12.0)	9.7 (7.2-12.7)	9.8 (7.6-13.1)	9.3 (7.4-12.0)	**0.02**
CMV constellation					
- High risk	270 (19%)	64 (18%)	80 (18%)	27 (17%)	
- Intermediate risk	847 (61%)	225 (64%)	283 (62%)	101 (66%)	0.70
- Low risk	269 (19%)	62 (18%)	90 (20%)	27 (17%)	
- unknown	18 (1%)	2	3	-	
Pre-transplant HLA-DSA	247 (18%)	55 (16%)	88 (19%)	37 (24%)	0.13
AB0 incompatible	89 (6%)	24 (7%)	30 (7%)	10 (6%)	0.99
A/B/DRB1 mismatches (n=2368)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)	0.92
A/B/DRB1-5/DQB1 mismatches (n=1905)	5 (4-7)	5 (4-7)	5 (4-6)	5 (3-7)	0.26
Induction therapy					
- ATG/Thymoglobulin	304 (22%)	81 (23%)	129 (28%)	45 (29%)	0.05
- Basiliximab	1060 (75%)	262 (74%)	315 (69%)	103 (66%)	

- None	40 (3%)	10 (3%)	12 (3%)	7 (5%)	
Maintenance immunosuppression - CyA/MPA/Pred - FK/MPA/Pred - Other	 249 (18%) 1111 (79%) 44 (3%)	 53 (15%) 293 (83%) 7 (2%)	 75 (16%) 371 (82%) 10 (2%)	 31 (20%) 117 (75%) 7 (5%)	0.36
Transplant Center - #1 (culture at each visit for first 6 months) - #2 (prolonged AB prophylaxis) - #3 - #4 - #5 - #6	 63 (26%) 181 (67%) 180 (43%) 145 (76%) 421 (71%) 414 (64%)	 82 (33%) 22 (8%) 125 (30%) 8 (4%) 24 (4%) 92 (14%)	 78 (31%) 44 (17%) 87 (21%) 30 (16%) 111 (19%) 106 (16%)	 25 (10%) 22 (8%) 26 (6%) 8 (4%) 33 (6%) 41 (6%)	**<0.001**

ADPKD = autosomal polycystic kidney disease, RRT= renal replacement therapy, HD = Hemodialysis, PD = Peritoneal Dialysis, CMV = cytomegalovirus, HLA-DSA = donor-specific HLA-antibodies, ATG = anti-T cell globulin, Tac = tacrolimus, MPA = mycophenolic acid, Pred = prednisone, AB = antibiotic.

Table 2. First-year outcomes.

Parameter	**Total (n=2368)**	**No colonization or UTI (n=1404)**	**Colonization only (n=353)**	**1-2 UTI (n=456)**	**≥3 UTI (n=155)**	**p-Value**
Graft loss or death	123 (5.2%)	80 (5.7%)	12 (3.4%)	24 (5.3%)	7 (4.5%)	0.36
Death	49 (2.1%)	27 (1.9%)	5 (1.4%)	12 (2.6%)	5 (3.2%)	0.45
Graft Loss	74 (3.1%)	53 (3.8%)	7 (2.0%)	12 (2.6%)	2 (1.3%)	0.13
eGFR [ml/min]	53 (41-66)	54 (42-67)	53 (43-67)	51 (39-66)	44 (34-58)*	**<0.001**
Patients with eGFR <25	107 (4.5%)	50 (3.6%)	8 (2.3%)	30 (6.6%)	19 (12.3%)	**<0.001**
Number of biopsies - none - one - two - more than two	 982 (41.5%) 774 (32.7%) 429 (18.1%) 183 (7.7%)	 571 (40.7%) 435 (31.0%) 268 (19.1%) 130 (9.2%)	 169 (47.9%) 134 (38.0%) 42 (11.9%) 8 (2.2%)	 185 (40.6%) 144 (31.6%) 93 (20.4%) 34 (7.4%)	 57 (36.8%) 61 (39.3%) 26 (16.8%) 11(7.1%)	**<0.001**

Number of rejections						
- none	1917 (81.0%)	1144 (81.5%)	295 (83.6%)	358 (78.5%)	120 (77.4%)	
- one	342 (14.4%)	199 (14.2%)	45 (12.7%)	72 (15.8%)	26 (16.8%)	0.38
- two	75 (3.2%)	38 (2.7%)	12 (3.4%)	18 (4.0%)	7 (4.5%)	
- more than two	34 (1.4%)	23 (1.6%)	1 (0.3%)	8 (1.7%)	2 (1.3%)	
Most severe TCMR						
- IA	109 (4.6%)	73 (3.1%)	11 (3.1%)	18 (3.9%)	7 (4.5%)	
- IB	11 (0.5%)	7 (0.5%)	-	3 (0.7%)	1 (0.6%)	0.58
- IIA	198 (8.4%)	113 (8.0%)	30 (8.5%)	41 (9.0%)	14 (9.0%)	
- IIB	17 (0.7%)	8 (0.6%)	3 (0.8%)	6 (1.3%)	-	
- III	5 (0.2%)	4 (0.3%)	-	1 (0.2%)	-	
Most severe ABMR						
- Acute/active ABMR	130 (5.5%)	67 (4.8%)	17 (4.8%)	31 (6.8%)	15 (9.7%)	0.76
- Chronic active ABMR	18 (0.8%)	9 (0.6%)	3 (0.8%)	5 (1.1%)	1 (0.6%)	
- Susp. for active ABMR	2	1	1	-	-	

* vs no colonization or UTI ($p<0.001$), vs colonization only ($p<0.001$), vs 1-2 UTI ($p=0.002$)

Table 3. Multivariable Cox regression model. One hundred and thirty death-censored graft failures occurred in 2245 patients having a functioning allograft at one-year post-transplant. The model is corrected for transplant centers.

Variable	HR (95%CI)	p-Value
UTI phenotype at one-year post-transplant		
- No colonization or UTI	Reference	
- Colonization only	1.00 (0.55-1.81)	0.98
- 1-2 UTI	1.52 (0.93-2.47)	0.10
- ≥3 UTI	4.41 (2.53-7.68)	**<0.001**
Urosepsis in the first year	0.74 (0.37-1.47)	0.39
Recipient age (per decade)	0.87 (0.75-1.01)	0.07
Recipient renal disease		
- Other nephropathy	Reference	
- ADPKD	0.95 (0.59-1.54	0.83
- Diabetic nephropathy	1.59 (0.88-2.87)	0.12
- Reflux/pyelonephritis	0.64 (0.25-1.61)	0.34
Male sex	2.21 (1.44-3.37)	**<0.001**
Donor age (per decade)	1.47 (1.27-1.70)	**<0.001**
Deceased Donor	1.93 (1.28-2.90)	**0.001**
CMV replication within first year	1.44 (1.00-2.06)	0.05
BKV replication within first year	1.16 (0.75-1.79)	0.50
Pre-transplant HLA-DSA	1.73 (1.12-2.66)	**0.01**
A/B/DRB1-Mismatches (per mismatch)	0.98 (0.86-1.12)	0.98
Number of rejections within first year		
- none	Reference	
- one	1.88 (1.15-3.06)	**0.01**
- two or more	3.00 (1.61-5.62)	**<0.001**
ABMR within the first year	1.40 (0.75-2.61)	0.29

Table 4. Comparison of patients with occasional (1-2 UTI) and recurrent UTI (≥3 UTI).

Parameter	1-2 UTI (n=456)	≥3 UTI (n=155)	p-value
Number of colonization(s)			
- none	250 (55%)	63 (41%)	**<0.001**
- one	113 (25%)	38 (25%)	
- more than one	93 (20%)	54 (34%)	
Patients with urosepsis	61 (13%)	45 (29%)	**<0.001**
Recipient age	57 (46-65)	58 (47-65)	0.88
Female sex	237 (52%)	91 (59%)	0.16
Recipient renal disease			
- ADPKD	103 (23%)	33 (21%)	
- Diabetic Nephropathy	46 (10%)	15 (10%)	0.68
- Reflux/Pyelonephritis	33 (7%)	16 (10%)	
- Other	274 (60%)	91 (59%)	
Donor age	56 (43-65)	54 (45-64)	0.67
Deceased donor	290 (64%)	105 (68%)	0.38
Pre-transplant HLA-DSA	88 (19%)	37 (24%)	0.25
AB0 incompatible	30 (7%)	10 (6%)	1.00
A/B/DRB1 mismatches (n=611)	4 (3-5)	4 (3-5)	0.99
A/B/DRB1-5/DQB1 mismatches (n=458)	5 (4-6)	5 (3-7)	0.91
Induction therapy			
- ATG/Thymoglobulin	129 (28%)	45 (29%)	0.48
- Basiliximab	315 (69%)	103 (66%)	
- None	12 (3%)	7 (5%)	
Maintenance immunosuppression			
- CyA/MPA/Pred	75 (16%)	31 (20%)	0.17
- FK/MPA/Pred	371 (82%)	117 (75%)	
- Other	10 (2%)	7 (5%)	
Transplant Center			
- #1 (culture @ each visit first 6 mt)	78 (76%)	25 (24%)	
- #2 (prolonged AB prophylaxis)	44 (67%)	22 (33%)	0.56
- #3	87 (77%)	26 (23%)	
- #4	30 (79%)	8 (21%)	
- #5	111 (77%)	33 (23%)	

- #6	106 (72%)	41 (28%)	

ADPKD = autosomal polycystic kidney disease, HLA-DSA = donor-specific HLA-antibodies, ATG = anti-T cell globulin, Tac = tacrolimus, MPA = mycophenolic acid, Pred = prednisone.

Figure legends

Figure 1. Overview of the frequency/incidence and temporal distribution of infection phenotypes observed within the first-year post-transplant.

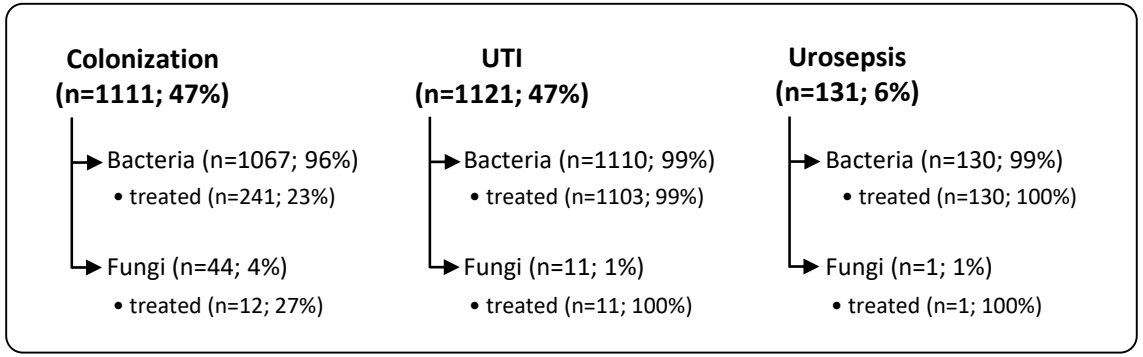
Figure 2. Overview and temporal distribution of detected bacteria/fungi according to infection phenotype.

Figure 3. Long-term patient and death-censored allograft survival among 2245 patients having a functioning allograft at one-year post-transplant, grouped by UTI phenotypes observed within the first-year post-transplant.

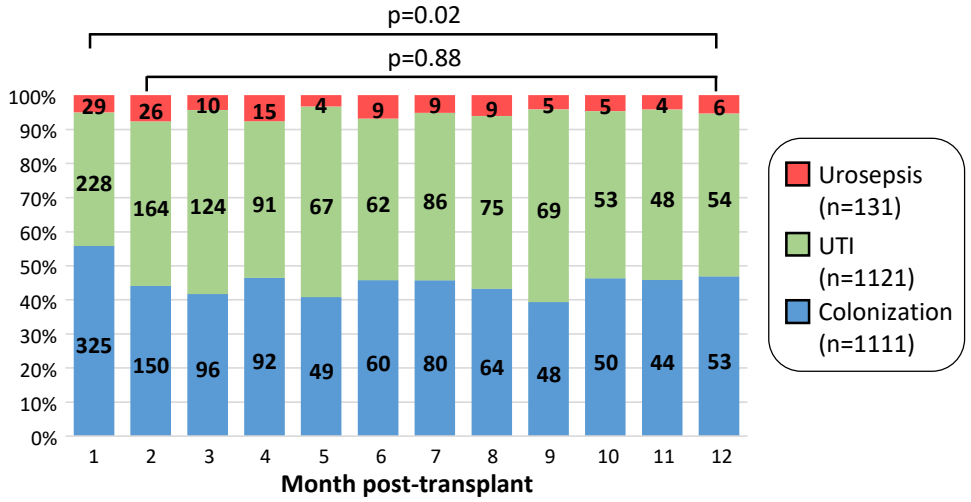
Figure 4. Distribution of pathogens observed in the '1-2 UTI' and '≥3 UTI' groups, stratified by the infection phenotype.

Figure 1

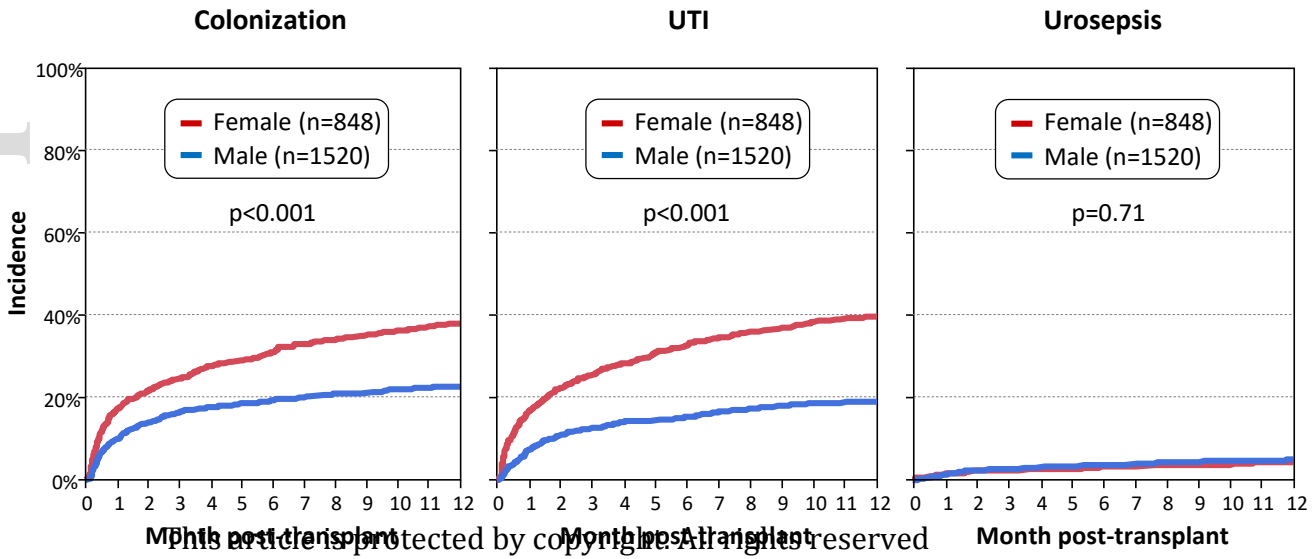
A UTI events (n=2363)



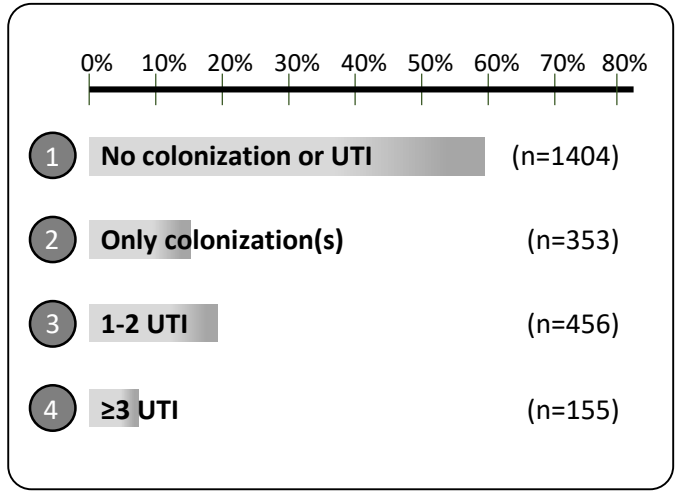
B Temporal distribution of UTI events (n=2363)



C Incidence of UTI events, grouped by sex



D Patients (n=2368) grouped according to all UTI events recorded within the first year post-transplant



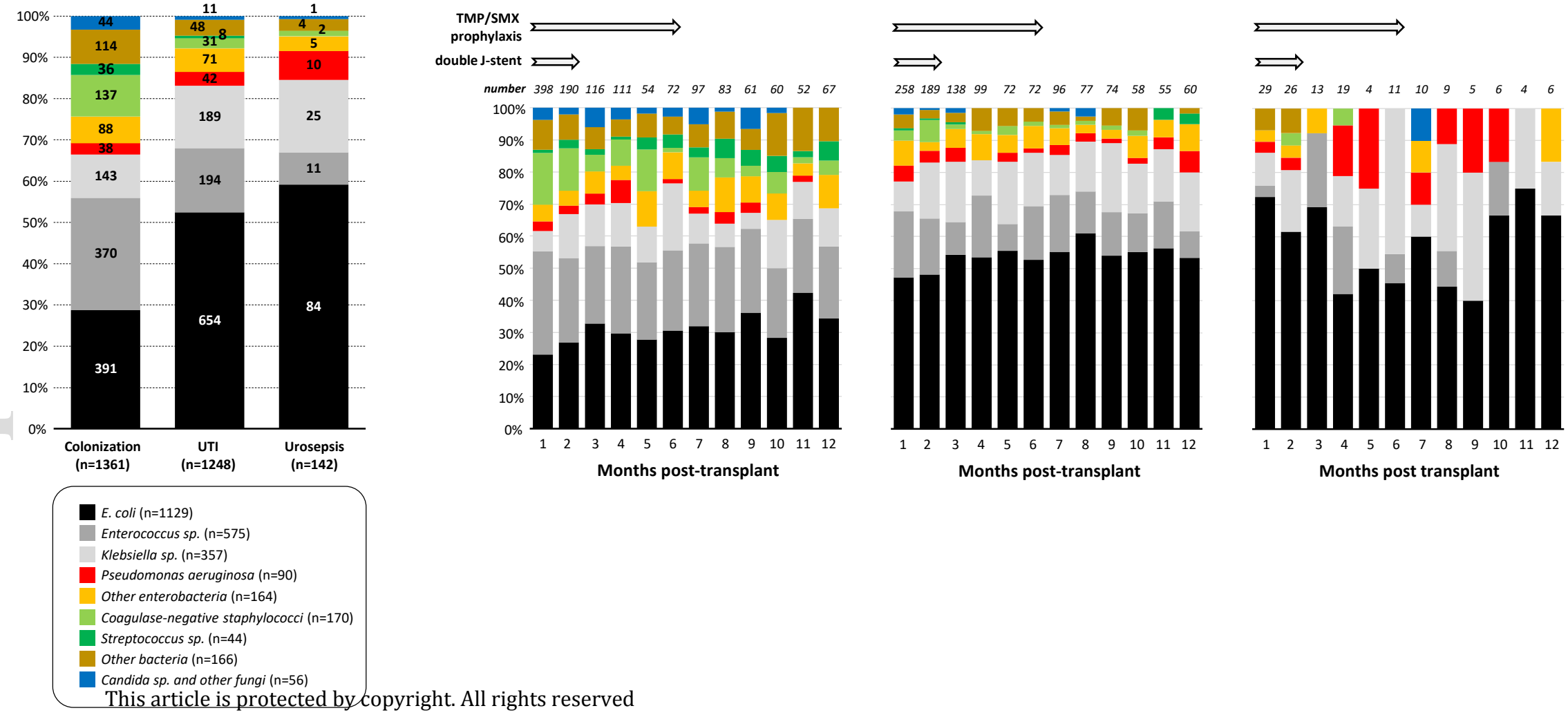
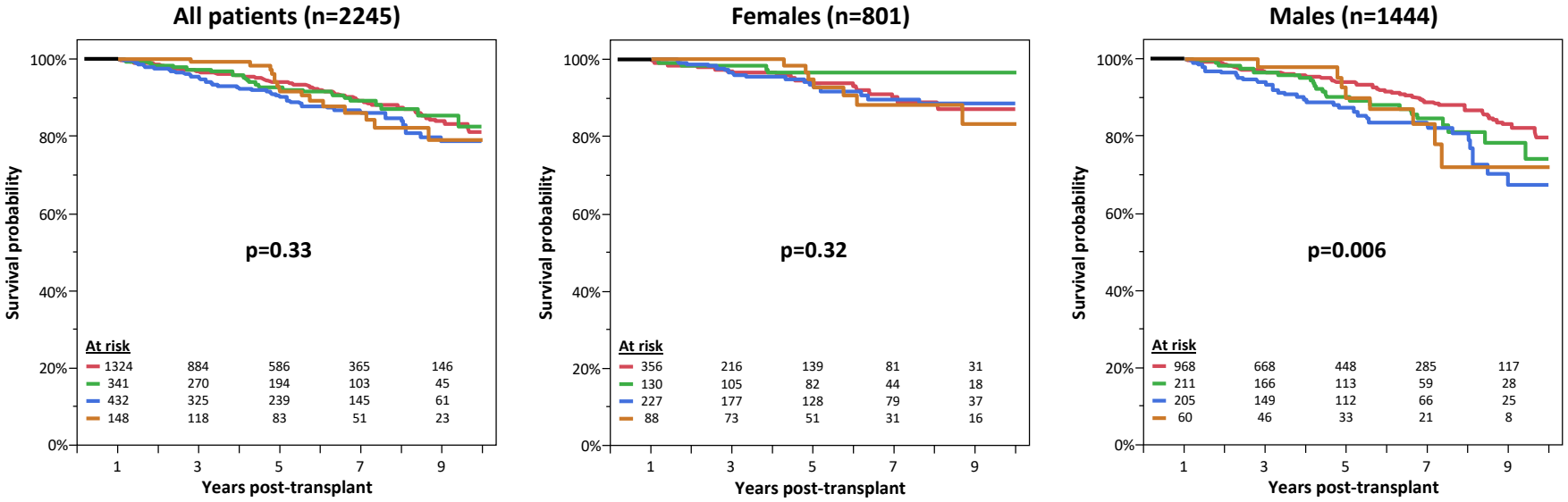


Figure 3

A Patient survival



B Death-censored graft survival

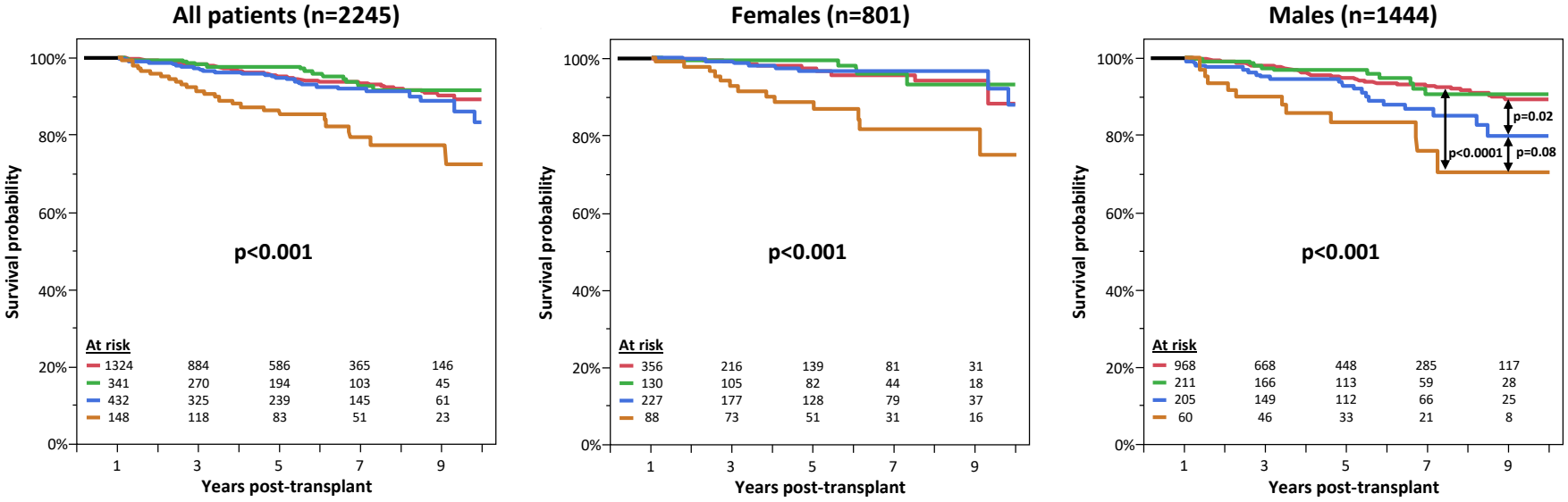


Figure 4