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Incidences of Infectious Events in a Renal Transplant Cohort of the German Center of Infectious Diseases (DZIF)

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Background. Infectious complications are a major cause of morbidity and mortality after kidney transplantation.

Methods. In this transplant cohort study at the German Center of Infectious Diseases (DZIF), we evaluated all infections occurring during the first year after renal transplantation. We assessed microbial etiology, incidence rates, and temporal occurrence of these infections.

Results. Of 804 renal transplant recipients (65.2% male, 51 ± 14 years), 439 (54.6%) had 972 infections within the first year after transplantation. Almost half of these infections (47.8%) occurred within the first 3 months. Bacteria were responsible for 66.4% (645/972) of all infections, followed by viral (28.9% [281/972]) and fungal (4.7% [46/972]) pathogens. The urinary tract was the most common site of infection (42.4%). *Enterococcus* was the most frequently isolated bacterium (20.9%), followed by *E. coli* (17.6%) and *Klebsiella* (12.5%). *E. coli* was the leading pathogen in recipients <50 years of age, whereas *Enterococcus* predominated in older recipients. Resistant bacteria were responsible for at least 1 infection in 9.5% (76/804) of all recipients. Viral infections occurred in 201 recipients (25.0%). Of these, herpes viruses predominated (140/281 [49.8%]), and cytomegalovirus had the highest incidence rate (12.3%). In the 46 fungal infections, *Candida albicans* (40.8%) was the most commonly isolated. Other fungal opportunistic pathogens, including *Aspergillus fumigatus* and *Pneumocystis*, were rare.

Conclusions. Renal allograft recipients in Germany experience a high burden of infectious complications in the first year after transplantation. Bacteria were the predominating pathogen, followed by opportunistic infections such as cytomegalovirus. Microbial etiology varied between age groups, and resistant bacteria were identified in 10% of recipients.

Keywords. infection; renal transplantation; cohort study; German; DZIF.

Solid organ transplant recipients require long-term immunosuppression, which puts them at risk for life-threatening infections. Infectious diseases are a major cause of morbidity and mortality after kidney transplantation, especially in the early post-transplant period [1–3]. Infectious complications also reduce recipients' quality of life and increase health care costs [2, 4, 5]. Although infections play a fundamental role in recipient prognosis and allograft survival [6, 7], many questions regarding the prevention and early diagnosis of infections remain unanswered, and more

research is needed in this area. Post-transplant data are often restricted by a lack of both stringent patient follow-up and standardized definitions of infections. Very few prospective cohort studies of transplant recipients have investigated all infectious complications [8–12], and the occurrence and timeline of all post-transplantation infections have not been studied in a German transplant cohort.

To prevent infection and reduce infection-related morbidity and mortality, we need information on multiple factors. For example, immunosuppressive strategies can reduce the incidence of rejection but increase the recipients' susceptibility to infection [13–15]. Furthermore, the availability of efficient prophylaxis may have modified frequencies and temporal infection patterns [1, 9, 12]. Knowing the timing and frequency of infections in the era of extended donor/recipient criteria, modern immunosuppression, and routine use of prophylaxis is crucial for implementing prevention strategies.

The transplant cohort of the German Center of Infectious Diseases (DZIF) is a unique database that evaluates infections after renal transplantation [16]. In this cohort, clinical data are being collected, together with biosamples from transplant

recipients (predominantly renal allograft recipients). In this study, we assessed the microbial etiology, incidence rates, and temporal occurrence of all infections occurring in this cohort.

METHODS

Study Population and Design

The DZIF transplant cohort is a multicenter prospective cohort study at the German Center for Infection Research [16]. It includes allograft recipients from 5 of the largest German transplant centers (University Hospital Hannover, University Hospital and Renal Center Heidelberg, TU Munich, LMU Munich, and University Hospital Tuebingen). In participating transplant centers, all patients receiving organs were informed about the study and invited to participate.

In the present study, we analyzed data from all adult renal and simultaneous pancreas–kidney allograft recipients aged 18 years and older who consented to participate and received a transplant between April 2011 and November 2019. Ethics approval was obtained from all participating centers (Hannover Medical School Nr 6534, Medical Faculty of the University of Heidelberg Nr S-585/2013, Medical Faculty of the TU Munich Nr 5926/13, LMU Munich Nr 380-15, University Hospital Tuebingen Nr 327/2014BO1), and all participants provided written informed consent.

Study visits were performed immediately before transplantation and at months 3, 6, 9, and 12 after transplantation. We also performed study visits when infections were detected. At each study visit, clinical and laboratory data were collected and entered into a central web-based database. The DZIF transplant cohort monitors data and conducts quality audits regularly, and the study was approved by the DZIF Scientific Steering Committee.

Patient Consent

Ethics approval was obtained from all participating centers (Hannover Medical School Nr 6534, Medical Faculty of the University of Heidelberg Nr S-585/2013, Medical Faculty of the TU Munich Nr 5926/13, LMU Munich Nr 380-15, University Hospital Tuebingen Nr 327/2014BO1), and all participants provided written informed consent.

Outcomes

The primary outcome was the occurrence of clinically relevant infection within the first 12 months after transplantation. Infections were categorized as clinically relevant if the patient complained about specific clinical symptoms (eg, fever, malaise, pain) or if the patient was hospitalized and had antibiotic, antiviral, or antifungal treatment in therapeutic doses. Secondary outcomes were the type of pathogen, timing of infection, and site of infection.

Infectious Events

All infections were identified by trained transplant physicians using paper-based or electronic hospital records and referral

documentation. Infections were defined according to Kidney Disease: Improving Global Outcomes (KDIGO) 2009 guidelines, AST 2019 infection guidelines, and European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group definitions [17–20].

A urinary tract infection was only included in case of clinical symptoms in addition to a positive urine culture [18]. Antimicrobial resistance was also recorded [21]. Herpes virus and polyomavirus infections were detected by real-time polymerase chain reaction. BK virus above the threshold of 10^4 copies per mL plasma was defined as clinically significant [17]. Fungal infections were reported if they met EORTC/MSG criteria with proven and probable invasive infection [19, 20]. We included all proven and probable fungal infections and fungemias. *Pneumocystis jirovecii* infection was diagnosed by sputum culture and bronchial lavage.

Donor-Derived Infection

Immunosuppression

Almost all patients received a standard triple-drug combination (comprising a calcineurin inhibitor, mycophenolate, and steroids) together with an interleukin 2 receptor antagonist (basiliximab) to induce immunosuppression.

Prophylaxis and Surveillance Strategy

Prophylaxis and surveillance strategy was suggested to be performed according to KDIGO 2009 guidelines [17]. Standard protocol included antiviral prophylaxis with valganciclovir for all cytomegalovirus (CMV) immunoglobulin G (IgG)–positive recipients and for all recipients of organs from CMV IgG–positive donors for at least 3 months. In case of the high-risk constellation D+/R–, 6 months of prophylaxis was suggested. If the recipient was CMV IgG positive, 3-month valganciclovir prophylaxis was recommended. *Pneumocystis jirovecii* infection was prevented with trimethoprim-sulfamethoxazole for 6 months. Anti-*Candida* prophylaxis with oral nystatin was provided within the first 1–3 months if >20 mg of methylprednisolone was administered. Urinary tract infection prophylaxis was suggested with trimethoprim-sulfamethoxazole for 6 months after transplantation. Screening for BKV was was recommended to be performed monthly for the first 6 months and every 3 months thereafter as well as in case of worsening of allograft function. No routine EBV screening was performed. Urinary tract infection surveillance was routinely performed with urine culture at each visit, in addition to recording clinical symptoms.

Recipients who received organs from bacteremic or fungemic donors had targeted antimicrobial therapy for a period of 7–14 days.

Statistical Analysis

It was assumed that all 5 centers together cover at least 20% of all solid organ transplants in Germany and provide a high number of infectious events, allowing in-depth analysis of infectious complications. The time of observation was defined as the time between transplantation and transplant failure, loss to follow-up, death, or 12 months after the transplant—whichever occurred first. Cumulative infection rates were calculated as the percentage of infected patients during the first year post-transplantation. According to respective data distribution, continuous variables were expressed as means and SDs or as medians and interquartile ranges (IQRs). Categorical variables were presented as numbers and percentages. Continuous variables were compared using the Mann-Whitney U test or Student t test, as appropriate. Crosstabs combined with the chi-square test or Fisher exact test was used to compare categorical variables. Statistical significance was defined as a P value <.05. We performed logistic regression to evaluate independent risk factors for the occurrence of multiple infections. Significant variables in univariate analysis were introduced in a multivariate model. Cox regression was used to analyze the effect of preceding infections depending on pathogen class (bacterial/viral fungal). Any preceding infection within the first year was considered a time-dependent covariate. Highly prevalent pathogens in patients suffering multiple infections were detected by logistic regression, thereby comparing first-year cumulative incidence rates of patients suffering >2 infections/year with those of patients suffering 1 or 2 infection(s)/year. All statistical analyses were performed using IBM SPSS Statistics, version 28.0 for Mac OS X (SPSS, Inc. Chicago, IL, USA).

RESULTS

Renal Allograft Recipients and Incidence of Infections

All adult renal transplant recipients consenting to participate in the DZIF transplant cohort and receiving a transplant in 1 of the 5 recruiting centers between April 2011 and November 2019 (n = 804) were enrolled for our analysis; 65.2% were male, and the mean age was 51 ± 14 years (Tables 1 and 2). Forty-two (5%) patients had a simultaneous pancreas–kidney transplantation. Follow-up was terminated early in 39 patients (15 patients died, 15 had transplant failure, and 9 were lost to follow-up). Infections were recorded as the direct cause of death in 6/15 patients (40%; pneumonia due to *Pseudomonas* in 1 patient, invasive aspergillosis in 2 patients, invasive mucormycosis in 1 patient, bornavirus encephalitis in 1 patient, and an outpatient infection of unknown origin in 1 patient).

Standard prophylaxis included 6-month anti-*Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole for all recipients. Anti-*Candida* prophylaxis (mostly oral nystatin) was given to 70.2% of recipients for 1–3 months. Antiviral prophylaxis (valganciclovir/ganciclovir) was provided to 74.9% of all recipients for at least 3 months.

Burden and Timeline of Infections

In total, 972 infections were recorded in 439 patients within the first year after renal transplantation, resulting in a cumulative incidence rate of 54.9% (439/804) or 2.2 (range, 1–11) infections per infected patient (Figure 1). Infection rates were highest in the first month after transplantation at 21.1% (205/972; 8.3 episodes per 1000 transplant-days); 47.8% (465/972) of infections occurred within the first 3 months (6.4 episodes per 1000 transplant-days), 25.3% (246/972) between months 3 and 6, 15.3% (149/972) between months 6 and 9, and 11.5% (112/972) between months 9 and 12.

Nosocomial infections (mostly bacterial urinary tract) predominated in the first months, followed by opportunistic viral infections such as CMV and BK virus (BKV) between months 1 and 5 (Figure 1). There were 2 peaks of fungal infection. *Candida* spp. and *Aspergillus fumigatus* were the leading pathogens in the first 2 months, while *Pneumocystis jirovecii* occurred after month 4. There was no difference in the incidence of infections between male and female recipients (male 54.2%, female 58.2%; P = .28). However, age affected the incidence of infection, with recipients aged >65 years having an increased risk of bacterial and fungal infection (Tables 1 and 2; Supplementary Figure 2).

Bacterial Infections

Bacteria accounted for 66.4% (645/972) of all infections (Figure 1, Table 3). A bacterial infection was reported in 41.3% (332/804) of all recipients (male 36.3%, female 44.7%; P = .28), and the incidence increased with recipients' age (<50 years: 35.2%; 50–65 years: 43.9%; >65 years: 48.9%) (Supplementary Figures 1 and 2). Elderly recipients tended to experience bacterial infections later than younger recipients did (median [IQR], 39 [17–85] days vs 28 [11–131] days; P = .064). Regarding location of infection, bacterial infections were most common in the urinary tract (62.3% [402/645]), followed by the respiratory tract (8.2% [53/645]) and gastrointestinal tract (7.0% [45/645]). Bacteremia was noticed in 3.5% (34/972) of all infections, concerning 31 patients (3.9%), and *E. coli* was the predominant pathogen (35.7%); 54.9% (354/645) of infections occurred within the first 3 months. *Enterococcus* spp. predominated within the first month, and gram-negative bacteria (especially *E. coli, Klebsiella* spp.) predominated within months 3 and 6.

Enterococcus was isolated most often (20.9% [161/771]), followed by *E. coli* (17.6% [136/771]) and *Klebsiella* (12.5% [96/771]). *E. coli* was the predominant pathogen among recipients aged <50 years, whereas *Enterococcus* species were the most frequent among recipients aged 50–65 and >65 years (Supplementary Figure 3). The percentage of *Pseudomonas*

Table 1. Characteristics of Recipients, Donors, and Antimicrobial Prophylaxis

	Total	Data Complet-eness	I <50 Years	II 50–65 Years	III >65 Years	Male	Female
Total No. of patients	804		315	351	137	515	275
Demographics							
Age at tx, mean ± SD, range, y	51 ± 14 18–79	99.0	37 ± 8 18–49	57 ± 5 50–65	69 ± 3 66–79	52 ± 14 18–79	50 ± 14 18–74
Male gender	515 (65.2)	98.3	64.2[a]	62.1	75.0[a]	100.0	0.00
Clinical data							
Cause of ESRD		99.0					
Glomerulonephritis	247 (31.0)		32.1	31.9	26.5	34.5	25.5
APKD	122 (15.3)		10.9	21.6	9.6	12.4	20.1
Diabetes mellitus	84 (10.6)		10.3	9.8	13.2	11.0	9.5
Nephrosclerosis	43 (5.4)		2.2	6.3	10.3	6.3	4.0
Interstinal nephritis	25 (3.1)		3.5	2.9	5.1	3.1	3.3
Vasculitis and collagenoses	24 (3.0)		2.6	3.2	3.7	2.0	5.1
Urologically caused diseases	24 (3.0)		4.8	0.9	2.9	2.5	2.9
Other hereditary diseases	38 (4.8)		9.0	2.6	0.7	5.5	3.6
Other	192 (24.1)		24.7	21.0	30.9	22.7	25.9
Body mass index, mean ± SD, kg/m^2	26 ± 5	97.8	25 ± 5	26 ± 5	27 ± 5	25 ± 3	25 ± 5
Donor characteristics							
Deceased donor	522 (65.7)	98.9	47.3[b]	73.3[b]	88.8[b]	64.2	68.0
Age group		95.8					
<35 y	78 (10.1)		13.7	10.0	2.3	8.9	12.4
≥35–<60 y	363 (47.1)		61.7	48.7	9.9	47.9	45.1
≥60 y	329 (42.7)		24.7	41.3	87.8	43.2	42.5
Male sex	330 (42.8)	95.9	41.0	44.4	42.7	39.9	47.7
CMV serologies							
R+	407 (54.8)	92.4	55.1	49.0	58.6	51.8[g]	60.4[g]
D+	445 (58.1)	95.3	58.7	54.7	59.1	58.0	58.3
D+/R−	157 (22.0)	88.9	21.3	20.2	21.7	37.0	21.6
Immunized							
AB0 incompatibility	45 (5.9)	95.4	6.6	5.7	2.9	5.6	5.1
Prior transplant	126 (15.7)	100.0	19.0	14.2	10.9	15.1	16.7
Pancreas–kidney transplantation	42 (5.2)	99.1	8.2[c]	4.6[c]	1.5[c]	6.0	5.4
Antimicrobial prophylaxis							
Antiviral[d]	568 (74.9)	94.3	76.6	73.6	74.6	73.5	78.3
Anti-*Candida*[e]	521 (70.2)	93.0	70.3	72.0	65.3	72.0	67.7
Postoperative variables							
In-patient stay, median (IQR), d	18 (14–25)	98.1	16 (13–24)	18 (14–25)	21 (15–31)	19 (14–26)	17 (14–24)
Delayed graft function	126 (15.9)	98.4	13.3[f]	16.0	21.8[f]	15.4	16.8

Data presented as No. (%) or as % (columns 3–8) unless otherwise indicated. Missing data were excluded. Delayed graft function = need for hemodialysis within the first 7 days post-transplantation.

Abbreviations: APKD, autosomal polycystic kidney disease; CMV, cytomegalovirus; D+, donor negative; ESRD, end-stage renal disease; IQR, interquartile range; R+, recipient positive; R–D+, recipient negative, donor positive; tx, transplantation.

[a]Statistically significant result, tested with chi-square test: $P = .025$, $\chi^2 = 5.03$.

[b]Statistically significant result, tested with chi-square test: I vs III: $P < .001$, $\chi^2 = 67.26$; I vs II: $P < .001$, $\chi^2 = 46.78$.

[c]Statistically significant result, tested with chi-square test: I vs II: $P = .014$, $\chi^2 = 6.04$; I vs III: $P = .003$, $\chi^2 = 9.01$.

[d]Mostly valganciclovir/ganciclovir.

[e]Mostly oral nystatin.

[f]Statistically significant result, tested with chi-square test: I vs III: $P = .023$, $\chi^2 = 5.15$.

[g]Male vs female: $p = .026$, $\chi^2 = 4.95$.

aeruginosa infections increased with age, and the rate of infection was almost 4 times higher in recipients >65 years old than in recipients <50 years old (14.5% vs 3.7%). *Pseudomonas* infection was also more common in males than in females (6.6% vs 2.2%; $P = .007$), whereas *E. coli* was more frequently detected in females (*E. coli* 17.4% vs 10.9%; $P = .010$).

Resistant bacteria were highly prevalent, involved in 19.1% (123/645) of all bacterial infections and affecting 9.5% (76/804) of our cohort. This rate was nearly 3 times higher in recipients aged >65 years than in recipients aged <50 years (16.1% [22/137] vs 5.4% [17/315]; $P < .001$). Of the bacteria we isolated from recipients, 16.0% (123/771) were resistant strains. Vancomycin-resistant *Enterococcus* was the most predominant resistant bacteria (44.7% [55/123]), followed by multiresistant gram-negative bacteria (26.0% [32/123]). Opportunistic bacteria, such as

Table 2. Characteristics of Infected Patients

	Bacterial Infection	Viral Infection	Fungal Infection
Total No. of patients	332	201	39
Demographics			
Age at tx, mean ± SD, range, y	53 ± 14, 18–79	51 ± 14, 20–79	58 ± 12, 27–76
Male gender	63.0	65.7	66.7
Clinical data			
Cause of ESRD			
Glomerulonephritis	27.4	33.3	17.9
APKD	16.9	14.9	5.1
Diabetes mellitus	12.0	8.5	25.6
Nephrosclerosis	5.7	4.0	15.4
Interstinal nephritis	3.0	5.0	5.1
Vasculitis and collagenoses	2.1	4.5	2.6
Urologically caused diseases	3.0	2.0	0.0
Other hereditary diseases	4.5	7.0	2.6
Other	25.3	20.9	25.6
Body mass index, mean ± SD, kg/m^2	26 ± 4	26 ± 4	26 ± 5
Donor characteristics			
Deceased donor	68.7	71.1	87.2
Age group			
<35 y	8.5	4.1	10.5
≥35–<60 y	42.9	30.6	31.6
≥60 y	48.6	26.5	57.9
Male sex	45.6	41.8	36.8
CMV serologies			
R+	55.4	49.2	45.9
D+	60.5	64.4	63.2
R+/D−	23.7	31.9	30.6
Immunized			
AB0 incompatibility	5.4	5.5	2.6
Prior transplant	16.6	16.4	12.8
Pancreas–kidney transplantation	6.0	4.5	17.9
Antimicrobial prophylaxis			
Antiviral[a]	76.5	78.4	74.4
Anti-*Candida*[b]	71.9	79.0	84.6
Postoperative variables			
In-patient stay, median (IQR), d	21, 15–30	18, 14–25	33, 16–40
Delayed graft function	20.1	18.0	44.7

Data presented as % unless otherwise indicated. Missing data were excluded. Delayed graft function = need for hemodialysis within the first 7 days post-transplantation.

Abbreviations: APKD, autosomal polycystic kidney disease; CMV, cytomegalovirus; D+, donor negative; ESRD, end-stage renal disease; IQR, interquartile range; R+, recipient positive; R−D+, recipient negative, donor positive; tx, transplantation.

[a]Mostly valganciclovir/ganciclovir

[b]Mostly oral nystatin.

Legionella spp., *Nocardia* spp., and *Mycobacteria* spp., were rare (0.6% [4/645]).

Viral Infections

Viral pathogens were responsible for 28.9% (281/972) of all infections (Figure 1, Table 4) and were detected in 25.0% (201/804) of recipients (25.6% male, 25.1% female; $P = .87$) (Supplementary Figures 1 and 2). Recipients aged >65 years were least affected by viral infections, and recipients aged 50–65 years were most affected (18.2% [25/137] vs 28.8% [101/351]; $P = .002$). This was particularly true for CMV infection, which had an incidence of 14.5% (51/351) in middle-aged recipients and 6.6% (9/137) in recipients >65 years old ($P = .016$). Of all viral infections, CMV had the highest incidence rate (12.3% [99/804]), being 3 times higher in the CMV high-risk group (D+/R−: 27.4% [43/157]) than in groups with a lower CMV risk (9.0% [50/558]; $P < .001$ [D−/R− = 0.6%, D+/R+ = 11.6%, D−/R+ = 12.9%]). In addition, the median (IQR) time to first CMV infection was significantly shorter in the high-risk group than in the lower-risk groups (106 [73–154] days vs 171 [82–251] days; $P = .022$), despite prophylaxis; 12.1% of all CMV-infected recipients were suffering from CMV
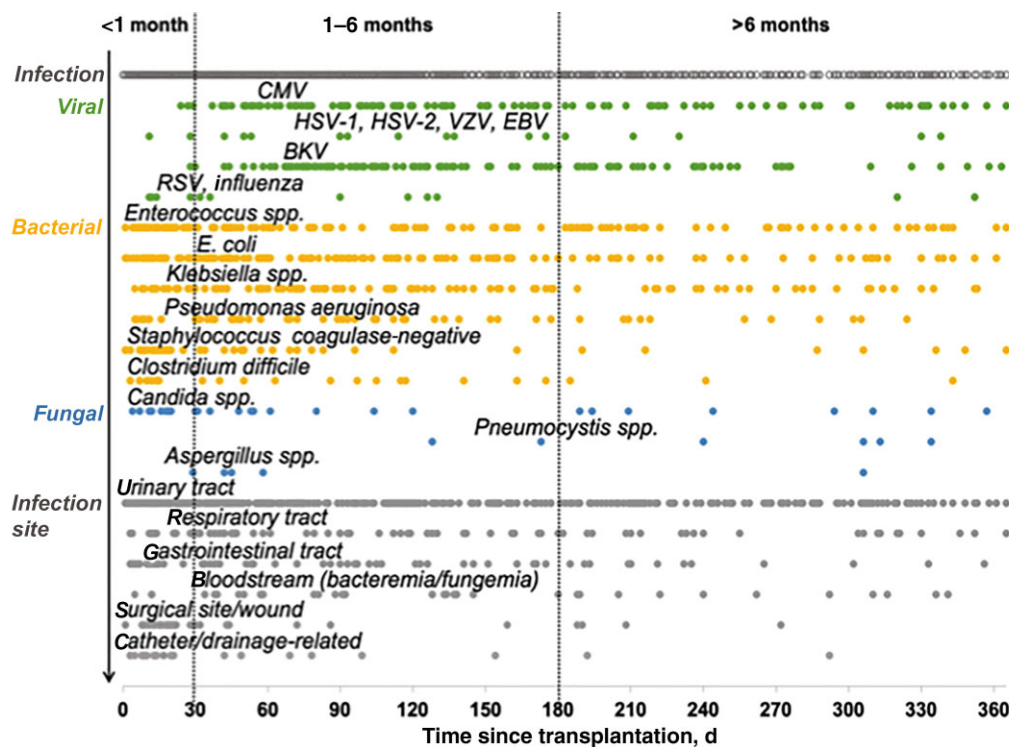
Figure 1. Infections detected in the first year after renal transplantation. Abbreviations: BKV, BK virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

disease. Herpesviridae other than CMV were more frequent in male recipients (12.8% vs 3.2%). In all, herpes viruses were predominant (140/281 [49.8%]). All recipients with herpes simplex virus (HSV) infection were male, and most (75% [6/9]) did not receive antiviral prophylaxis. The incidence of herpes infections also increased with age (<50 years: 5.0%; 50–65 years: 11.2%; <65 years: 16.2%). Polyomaviridae were the second most common viral pathogens (42.0% [118/281]), and of these, BKV was predominant (99.2% [117/118]). BKV nephropathy was confirmed in 1.5% (12/804) of all recipients. Notably, the temporal pattern of BKV and CMV infections was similar. Respiratory infections included influenza A and B (n = 8), respiratory syncytial virus (n = 6), and rhinovirus (n = 1) and were more common in female recipients than in male recipients (8.6% vs 3.6%). Gastrointestinal viral pathogens included hepatitis E (n = 2) and norovirus (n = 6).

Fungal Infections

There were 46 documented fungal infections (5.0% male, 4.7% female; $P = .84$) (Figure 1, Table 5). *Candida albicans* was the most common fungal agent and accounted for 40.8% (20/46) of all fungal isolates.

We documented 7 *Pneumocystis jirovecii* (14.3%) and 5 *Aspergillus fumigatus* infections (10.2%). *Aspergillus fumigatus* was only detected in males, particularly between months 1

and 2. Other opportunistic pathogens like *Cryptococcus neoformans* (n = 1) or Zygomycetes (n = 1) were rare.

Fungal infections were detected in 39/804 (4.9%) patients, and incidence rates increased with age (>65 years: 11.7%; vs <50 years: 1.9%; $P < .001$) (Supplementary Figures 1 and 2). The incidence of fungal infections was also high in pancreas–kidney allograft recipients (16.7% [9/42]). Of note, fungal infections were detected predominantly early in the youngest age group and predominantly late in the middle-aged group (median [IQR], 23 [13–35] days vs 128 [61–184] days; $P = .052$). The latest fungal infections were due to *Pneumocystis jirovecii* (median [IQR], 240 [151–310]), and the earliest were due to *Candida* non-*albicans* species (median [IQR], 25 [13–255]). Recipients infected with *Candida albicans* had a long postoperative stay (median [IQR], 45 [16–55] days), whereas recipients infected with non-*albicans* spp. (n = 12) were notably younger than those infected with other fungal pathogens (60 ± 9 vs 50 ± 14 years).

Almost 90% (34/39) of recipients with a fungal infection also had at least 1 bacterial infection during the first year after transplantation. In 80% (27/34) of cases, bacterial infection preceded fungal infection. All preceding bacterial infections were treated with broad-spectrum antibiotics (mostly carbapenems or glycopeptides). Only 4/39 (10.3%) patients with a fungal infection experienced no other infection within the first year. Overall, the

Table 3. Characteristics of Bacterial Infections

Bacterial Pathogen	No. of Bacterial Infections (Total = 645)	% of Bacterial Pathogen Detections (Total = 771)	First-Year Cumulative Incidence Rate, % (No. of Patients) (Total = 804)	Median Time to First Infection (IQR), d
All	645	771	54.6 (439)	34 (12–96)
Enterococcus spp.	161	20.9	14.8 (119)	31 (13–116)
E. coli	136	17.6	12.9 (104)	72 (24–153)
Unknown pathogen	137	17.7	13.2 (106)	74 (12–163)
Klebsiella spp.	96	12.5	7.8 (63)	72 (39–152)
Pseudomonas aeruginosa	56	7.3	5.0 (40)	89 (38–155)
Staphylococcus coagulase neg.	52	6.7	6.0 (48)	20 (13–64)
Enterobacter	23	3.0	2.7 (22)	102 (62–214)
Clostridium difficile	22	2.9	2.7 (22)	75 (14–135)
Other bacteria	19	2.5	2.2 (18)	46 (21–113)
Other gram-positive bacteria	19	2.5	2.4 (19)	58 (18–152)
Streptococcus/ Streptococcus spp.	11	1.4	1.4 (11)	181 (44–311)
Other Enterobacteria	16	2.1	1.9 (15)	75 (42–182)
Other nonenteric gram-neg. bac.	8	1.0	1.0 (8)	99 (48–140)
Staphylococcus aureus	8	1.0	0.9 (7)	71 (32–119)
Other mycobacteria	2	0.3	0.2 (2)	–
Stenostrophomonas	1	0.1	0.1 (1)	–
Pneumococcus	1	0.1	0.1 (1)	–
Legionella	1	0.1	0.1 (1)	–
Nocardia	1	0.2	0.1 (1)	–
Other anaerobic bacteria	1	0.2	0.1 (1)	–

Abbreviations: bac., bacteria; IQR, interquartile range.

mean number (range) of all infections per recipient was 4.2 ± 2.3 (1–11); 48.7% (19/39) were affected by resistant bacteria. The most common site of infection was the respiratory tract, mostly due to *Aspergillus fumigatus* and *Pneumocystis* spp.

Multiple Infections

More than 2 infections per year were detected in 17.0% (137/804) of recipients. The prevalence increased with age (25.5% in recipients aged >65 years vs 10.5% in recipients aged <55 years; *P* < .001). Univariate analysis revealed that recipient age, deceased donor, donor age, delayed graft function, and the number of postoperative inpatient-days were significantly associated with the occurrence of multiple infections (Table 6). Multivariate analysis confirmed that recipient age and number of postoperative inpatient-days were independent risk factors for multiple infections.

Table 7 shows pathogens that were significantly more prevalent in recipients with >2 infections per year than in recipients with 1–2 infections. Recipients infected with *Candida albicans* were frequently affected by multiple infections (mean [range], 5.0 [1–10] infections/patient), but also with resistant strains (66.7% [12/18]) (Figure 2).

Table 4. Characteristics of Viral Infections

Viral Infection	No. of Viral Infections (Total = 281)	% of Viral Pathogen Detections (Total = 281)	First-Year Cumulative Incidence Rate, % (No. of Patients) (Total = 804)	Median Time to First Infection (IQR), d
All	281	281	25.0 (201)	111 (71–183)
CMV	113	40.2	12.3 (99)	133 (74–219)
BKV	117	41.6	11.4 (92)	113 (84–182)
HSV-1	9	3.2	1.1 (9)	90 (42–114)
HSV-2	6[a]	2.1	0.7 (6)	45 (31–79)
VZV	6	2.1	0.7 (6)	172 (112–202)
Influenza A	6	2.1	0.7 (6)	79 (17–129)
RSV	6	2.1	0.7 (6)	34 (29–77)
Norovirus	6	2.1	0.7 (6)	65 (36–113)
EBV	5	1.8	0.6 (5)	137 (134–330)
Hepatitis E	2	0.7	0.2 (2)	–
Influenza B	2	0.7	0.2 (2)	–
HHV-6	1	0.4	0.1 (1)	–
JCV	1	0.4	0.1 (1)	–
Rhinovirus	1	0.4	0.1 (1)	–

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpes virus 6; HSV, herpes simplex virus; IQR, interquartile range; JCV, JC virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.
[a]All 6 patients had HSV-2 and HSV-1.

Table 5. Characteristics of Fungal Infections

Fungal Pathogen	No. of Fungal Infections (Total = 46)	% of Fungal Pathogen Detections (Total = 49)	First-Year Cumulative Incidence Rate, % (No. of Patients) (Total = 804)	Median Time to First Infection (IQR), d
All	46	49	39 (4.9)	58 (20–159)
Candida albicans	20	40.8	18 (2.2)	54 (23–116)
Candida non-*albicans* spp.	12	24.5	12 (1.5)	25 (13–255)
Pneumocystis jirovecii	7	14.3	7 (0.9)	240 (151–310)
Aspergillus fumigatus	5	10.2	5 (0.6)	45 (42–58)
Other	3	6.1	3 (0.4)	181 (117–237)
Cryptococcus neoformans	1	2.0	1 (0.1)	–
Zygomycetes	1	2.0	1 (0.1)	–

Abbreviation: IQR, interquartile range.

Bacterial infection increased the risk of fungal infection (hazard ratio [HR], 6.45; 95% CI, 3.23–12.90; $P < .001$), and fungal infection increased the risk for bacterial infection (HR, 3.50; 95% CI, 1.44–8.49; $P = .006$). The risk of viral infection was not affected by bacterial infection (HR, 1.13; 95% CI, 0.84–1.52; $P = .43$) or fungal infection (HR, 0.87; 95% CI, 0.44–2.62; $P = .89$).

DISCUSSION

Effective management of post-transplant infection relies on prevention, early diagnosis, and specific therapy [15, 22]. For this, detailed information on the incidence, microbial etiology, and timeline of infections is crucial. This is the first comprehensive study of a representative German renal transplant cohort comprising >800 patients evaluating all clinically relevant infections detected during the first year after transplantation.

Almost 55% of our cohort experienced at least 1 clinically relevant infection. Bacterial infections predominated (66%), followed by viral (29%) and fungal (<5%) pathogens. BKV and CMV were the most frequently identified opportunistic pathogens.

Three infection periods have been reported after solid organ transplantation: Nosocomial infections predominate in the first month, followed by opportunistic infections between months 1 and 6, and community-acquired infections after month 6 [2, 14]. We confirmed these results; *Enterococcus* spp. and *Candida* spp. infections mainly occurred during the first 30 days, and infections with opportunistic pathogens, like CMV and BKV, were highly prevalent in the intermediate period. Infections with *Pneumocystis jirovecii* were rare and occurred mostly in the late period, presumably because routine trimethoprim-sulfamethoxazole prophylaxis was administered for 6 months after transplantation. Only a few community-acquired respiratory infections occurred during the late period—most were detected in the first month after transplantation. This might be because pathogens are typically not evaluated in patients with mild symptoms who do not require hospitalization.

Long-term immunosuppression and antimicrobial therapy increased the incidence of resistant pathogens in transplant patients [23–25]. We identified resistant strains in 9.5% of all recipients and in 50% of patients with fungal infections. This

Table 6. Risk Factors for Multiple Infections

Covariates	Univariate Analyses			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age at tx, y	1.03	[1.02–1.05]	<.001	1.02	[1.00–1.04]	**.038**
Male sex	1.32	[0.86–2.02]	.21	…	…	
Cadaveric donation	1.67	[1.05–2.66]	**.029**	1.18	[0.68–2.06]	.547
Antiviral prophylaxis	1.40	[0.85–2.32]	.186	…	…	
Prior tx	1.21	[0.69–2.13]	.504	…	…	
Pancreas–kidney tx	1.27	[0.54–3.00]	.580	…	…	
Delayed graft function[a]	1.92	[1.18–3.15]	**.009**	1.20	[0.67–2.14]	.547
Donor age[b]	1.10	[1.02–1.18]	**.010**	1.04	[0.96–1.12]	.383
No. of inpatient-d[c]	1.32	[1.17–1.49]	<.001	1.25	[1.10–1.43]	**<.001**

Recipients with >2 infections/year (group 1, n = 137) were compared with recipients with 1–2 infection(s)/year (group 2, n = 302). Results are based on logistic regression analyses. Inclusion criteria for multivariate analysis: $P < .05$ in univariate analysis.

Abbreviations: OR, odds ratio; tx, transplantation.

[a]Need for hemodialysis within the first 7 days post-transplantation.

[b]In 5-year intervals.

[c]Post-transplantation, in 7-day intervals.

Table 7. Highly Prevalent Pathogens in Patients Suffering Multiple Infections

	OR	95% CI	P	Incidence Rate Group 1	Incidence Rate Group 2
Candida non-*albicans* spp.	23.70	[3.00–187.09]	.003	7.3 (10/137)	0.7 (2/302)
Candida albicans	19.86	[4.50–87.57]	<.001	11.7 (16/137)	0.7 (2/302)
EBV	9.05	[1.02–81.77]	.035	2.9 (4/137)	0.3 (1/302)
Pneumocystis jirovecii	5.68	[1.09–29.66]	.033	3.6 (5/137)	0.7 (2/302)
Klebsiella spp.	5.44	[5.44–9.59]	<.001	29.9 (41/137)	7.3 (22/302)
Pseudomonas aerguinosa	4.27	[2.71–8.40]	<.001	18.2 (25/137)	5.0 (15/302)
Enterococcus spp.	4.60	[2.94–7.21]	<.001	48.9 (67/137)	17.2 (52/302)
Staph. coag. negative	2.98	[1.62–5.48]	<.001	19.0 (26/137)	7.3 (22/302)
Enterobacter	2.80	[1.18–6.66]	.015	8.8 (12/137)	3.3 (10/302)
E. coli	2.64	[1.67–4.16]	<.001	36.5 (50/137)	17.8 (54/302)
CMV	1.80	[1.13–2.86]	.013	29.9 (41/137)	19.2 (58/302)

First-year pathogen incidence rates in patients suffering >2 infections/year (n = 137) were compared with those in patients suffering 1 or 2 infections/year (n = 302). Not significant: BK virus (*P* = .065), *Streptococcus* spp. (*P* = .090), *Staphylococcus aureus* (*P* = .140), herpes simplex virus–1 (*P* = .277), influenza A (*P* = .277), norovirus (*P* = .277), respiratory syncytial virus (*P* = .277), herpes simplex virus–2 (*P* = .297), *Clostridium difficile* (*P* = .314), varicella zoster virus (*P* = 0.393), *Aspergillus fumigatus* (*P* = .497).

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; OR, odds ratio; *Staph.* coag. negative, *Staphylococcus* coagulase negative.

might reflect the high prevalence of multiple infections requiring antimicrobial therapies.

An association between bacterial and fungal infections and resistant strains appears likely. Elderly recipients with prolonged postoperative hospitalization seem to be particularly vulnerable. Early and intensified surveillance is needed. This might also be appropriate for pancreas–kidney allograft recipients, appearing to be susceptible to early *Candida* infections,

or elderly males, who are prone to *Pseudomonas aeruginosa*. All these predominantly nosocomial pathogens, including the most frequently isolated agent, *Enterococcus*, were associated with the occurrence of multiple infections. There could be a direct effect due to pathogen-specific mechanisms or an indirect effect as a consequence of frequent hospitalizations and unsuccessful therapies. The interaction of both effects seems likely. The current bacterial spectrum, with *Enterococcus* and *E. coli*
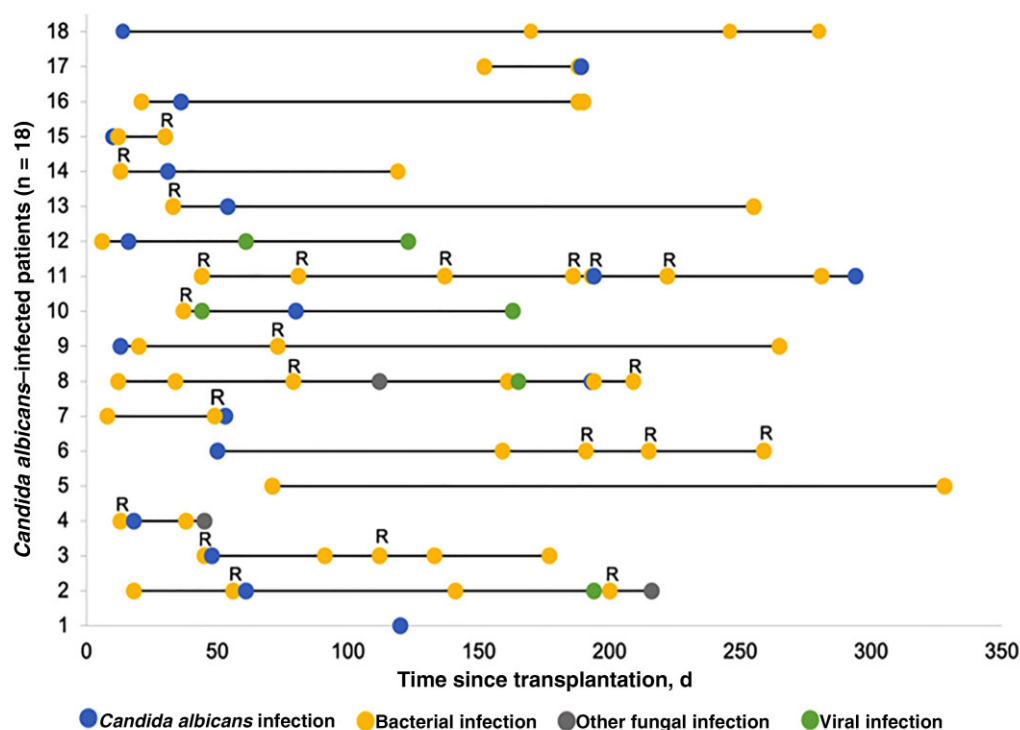

Figure 2. Patients with *Candida albicans* infections were frequently affected by multiple infections and resistant bacteria. Shown is a timeline of all infections during first year in renal allograft recipients with *Candida albicans* infection (n = 18). Abbreviation: R, bacterial resistance.

predominating, does not seem to be sufficiently covered by trimethoprim-sulfamethoxazole prophylaxis. Considering the high prevalence of bacterial infections, additional agents are required. Several new immunosuppressive regimens with varying immunosuppressive potential have been developed in the last years for transplant recipients [26, 27]. Opportunistic infections have been successfully reduced in these patients through prophylaxis and surveillance [2]. An important effect of these strategies is reducing the prevalence of *Pneumocystis jirovecii* and CMV infections, both of which peak at 4 months after transplantation. Patients receiving a CMV IgG–seropositive organs receive a 3- or 6-month valganciclovir prophylaxis [17, 28]. This is important because more than half of viral infections were herpes viruses, with CMV having the highest incidence rate. A prolonged CMV prophylaxis and/or an intensified pre-emptive strategy once valganciclovir is stopped could also be beneficial. Indeed, CMV infections remain an important risk factor for graft loss and patient mortality [29–31]. Another way to reduce CMV infection would be to test CMV-specific cell-mediated immunity in susceptible patients. This would allow CMV prophylaxis to be discontinued in individual patients [32]. BKV nephropathy is rare but can result in graft loss [33, 34]. In the DZIF cohort study, Polyomaviridae were the second most common viral pathogens, in agreement with findings from the Swiss Transplant Cohort [8]. Therapeutic interventions are limited, so strict surveillance, as suggested in the KDIGO guidelines, is needed [17].

Most clinical studies have focused on specific infections and have provided limited information on the global burden of infectious complications after renal transplantation [35–40]. This cohort study has collected data of optimal quality based on standardized definitions and quality audits [16], and these data guarantee a comprehensive view of all clinically relevant infections in the first year after renal transplantation. However, the generalizability of our results to other settings might vary depending on the geographic setting and distinct microbial prophylaxis strategy.

In conclusion, renal allograft recipients in Germany experienced a high burden of infectious events during the first year after transplantation. Current prophylactic agents appear efficient in the prevention of opportunistic infections, but thereby neglect common nosocomial infections (eg, *Enterococcus* spp.). The prevalence of nosocomial infections was high during the first months, and the prevalence of viral opportunistic infections such as CMV and BKV increased thereafter. Invasive fungal diseases and infections by opportunistic bacteria were rare. Many bacterial pathogens were multidrug resistant, supporting the need for specific microbiologic diagnoses and critical use of antibiotics. Age not only affects the frequency but also the temporal pattern and microbial etiology of infections. The occurrence of multiple infections was common and seems to correlate with immunodeficiency. Further research is needed to understand the effects and mechanisms of the frequently involved pathogens, first detected in the present study. Targeting these would be a very effective way to prevent further infections. In all, our observations may help to guide future surveillance strategies. Therefore, further prospective multicenter studies are required to verify and update our results and to pursue novel approaches for prophylactic strategies.

References

1. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med **2007;** 357:2601–14.
2. Fishman J. Infection in organ transplantation. Am J Transplant **2017;** 17:856–79.
3. Fiorentino M, Pesce F, Schena A, Simone S, Castellano G, Gesualdo L. Updates on urinary tract infections in kidney transplantation. J Nephrol **2019;** 32:751–61.
4. Martins BCC, Mesquita KHC, Costa I, et al. Hospital cost of complications after kidney transplant. Transplant Proc **2020;** 52:1294–8.
5. Bodro M, Linares L, Chiang D, Moreno A, Cervera C. Managing recurrent urinary tract infections in kidney transplant patients. Expert Rev Anti Infect Ther **2018;** 16:723–32.
6. Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. Am J Transplant **2015;** 15:3024–40.
7. Vogelzang JL, van Stralen KJ, Noordzij M, et al. Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry. Nephrol Dial Transplant **2015;** 30:1028–37.
8. van Delden C, Stampf S, Hirsch HH, 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:e159–69.
9. Juan R S, Aguado JM, Lumbreras C, et al. Incidence, clinical characteristics and risk factors of late infection in solid organ transplant recipients: data from the RESITRA study group. Am J Transplant **2007;** 7:964–71.
10. Koller MT, van Delden C, Müller NJ, 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;** 28:347–55.
11. Sousa SR, Galante NZ, Barbosa DA, Pestana JO. Incidence of infectious complications and their risk factors in the first year after renal transplantation. J Bras Nefrol **2010;** 32:75–82.

12. Garrido RS, Aguado JM, Díaz-Pedroche C, et al. A review of critical periods for opportunistic infection in the new transplantation era. Transplantation 2006; 82:1457–62.

13. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004; 351:2715–29.

14. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998; 338:1741–51.

15. Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect 2014; 20(Suppl 7):4–9.

16. Karch A, Schindler D, Kühn-Steven A, et al. The transplant cohort of the German Center for Infection Research (DZIF Tx-Cohort): study design and baseline characteristics. Eur J Epidemiol 2021; 36:233–41.

17. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9(Suppl 3): S1–155.

18. Goldman JD, Julian K. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33:e13507.

19. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008; 46:1813–21.

20. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020; 71:1367–76.

21. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18:268–81.

22. Marty FM, Rubin RH. The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy. Transpl Int 2006; 19:2–11.

23. Bodro M, Sabé N, Tubau F, et al. Risk factors and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in solid-organ transplant recipients. Transplantation 2013; 96:843–9.

24. Patel G, Rana MM, Huprikar S. Multidrug-resistant bacteria in organ transplantation: an emerging threat with limited therapeutic options. Curr Infect Dis Rep 2013; 15:504–13.

25. Ziakas PD, Pliakos EE, Zervou FN, Knoll BM, Rice LB, Mylonakis E. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. Am J Transplant 2014; 14:1887–94.

26. Kälble F, Schaier M, Schäfer S, et al. An update on chemical pharmacotherapy options for the prevention of kidney transplant rejection with a focus on costimulation blockade. Expert Opin Pharmacother 2017; 18:799–807.

27. Sommerer C, Suwelack B, Dragun D, et al. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney Int 2019; 96: 231–44.

28. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 2018; 102:900–31.

29. Leeaphorn N, Garg N, Thamcharoen N, Khankin EV, Cardarelli F, Pavlakis M. Cytomegalovirus mismatch still negatively affects patient and graft survival in the era of routine prophylactic and preemptive therapy: a paired kidney analysis. Am J Transplant 2019; 19:573–84.

30. Jehn U, Schütte-Nütgen K, Bautz J, et al. Cytomegalovirus viremia after living and deceased donation in kidney transplantation. J Clin Med 2020; 9:252.

31. Stern M, Hirsch H, Cusini A, et al. Cytomegalovirus serology and replication remain associated with solid organ graft rejection and graft loss in the era of prophylactic treatment. Transplantation 2014; 98:1013–8.

32. Kumar D, Chin-Hong P, Kayler L, et al. A prospective multicenter observational study of cell-mediated immunity as a predictor for cytomegalovirus infection in kidney transplant recipients. Am J Transplant 2019; 19:2505–16.

33. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 2002; 347:488–96.

34. Hirsch HH, Randhawa PS. BK polyomavirus in solid organ transplantation—guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33:e13528.

35. Moreno A, Cervera C, Gavaldá J, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. Am J Transplant 2007; 7: 2579–86.

36. Vidal E, Torre-Cisneros J, Blanes M, et al. Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort. Transpl Infect Dis 2012; 14:595–603.

37. Alevizakos M, Nasioudis D, Mylonakis E. Urinary tract infections caused by ESBL-producing Enterobacteriaceae in renal transplant recipients: a systematic review and meta-analysis. Transpl Infect Dis 2017; 19.

38. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 2010; 50:1101–11.

39. Brakemeier S, Dürr M, Bachmann F, Schmidt D, Gaedeke J, Budde K. Risk evaluation and outcome of Pneumocystis jirovecii pneumonia in kidney transplant patients. Transplant Proc 2016; 48:2924–30.

40. Illesy L, Szabo-Pap M, Toth F, et al. Bacterial infections after kidney transplantation: a single-center experience. Transplant Proc 2016; 48:2540–3.