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ORIGINAL ARTICLE

Infections after upper extremity allotransplantation: a worldwide population cohort study, 1998-2017

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SUMMARY

Risk-to-benefit analysis of upper extremity allotransplantation (UEA) warrants a careful assessment of immunosuppression-related complications. This first systematic report of infectious complications after UEA aimed to compare incidence and pattern of infections to that observed after kidney transplantation (KT). We conducted a matched cohort study among UEA and KT recipients from the International Registry on Hand and Composite Tissue Transplantation and the French transplant database DIVAT. All UEA recipients between 1998 and 2016 were matched with KT recipients (1:5) regarding age, sex, cytomegalovirus (CMV) serostatus and induction treatment. Infections were analyzed at three posttransplant periods (early: 0–6 months, intermediate: 7–12 months, late: >12 months). Sixty-one UEA recipients and 305 KT recipients were included. Incidence of infection was higher after UEA than after KT during the early period (3.27 vs. 1.95 per 1000 transplant-days, $P = 0.01$), but not statistically different during the intermediate (0.61 vs. 0.45/1000, $P = 0.5$) nor the late period (0.15 vs. 0.21/1000, $P = 0.11$). The distribution of infectious syndromes was significantly different, with mucocutaneous infections predominating after UEA, urinary tract infections and pneumonia predominating after KT. Incidence of infection is high during the first 6 months after UEA. After 1 year, the burden of infections is low, with favorable patterns.

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Introduction

The first successful upper extremity allotransplantation (UEA) performed in Lyon in 1998 heralded the era of reconstructive transplantation [1]. Since then, close to 100 patients have received UEA worldwide, with encouraging functional and aesthetic results [2–8]. Limb reconstructive transplantation is considered 'life-changing' as it substantially improves the quality of life of severely disabled persons [9,10]. However, because it is a 'nonlife-saving' procedure, its risk-to-benefit ratio must be carefully assessed.

The transplantation of multiple tissues from a genetically different donor exposes recipients to a high risk of allograft rejection [11,12]. It has been reported that more than 85% of vascularized composite allotransplantation (VCA) recipients have experienced at least one acute rejection (AR) episode during the first year posttransplant [5,13,14]. To prevent or treat rejection episodes, heavy immunosuppressive regimens are needed after VCA. In most cases, protocols are similar to those used in solid organ transplantation (SOT) [15]. Like SOT recipients, UEA recipients are thus exposed to the metabolic, malignant and infectious complications of lifelong immunosuppression.

Data on infectious complications after UEA are scarce and based on case reports or small cohort studies that address general outcome after UEA, which makes it difficult to assess the infectious risk in this population [13,16–26]. In SOT recipients, the incidence and types of infections depend on the type of transplanted organ, which accounts on the dissimilarities between the different SOT populations regarding ages, comorbidities, immunosuppression, surgical procedures or anatomical exposure of the allograft [27]. UEA recipients are young and disabled but otherwise healthy, and their allograft is sheltered from the environment by the skin barrier. For these reasons, one might hypothesize that UEA recipients are among the populations of allograft recipients with the lowest burden of infectious complications. Conversely, the infectious risk may be increased in UEA recipients who display a high incidence of AR episodes. These latter are readily recognized because of their visible nature and UEA recipients are probably exposed to higher cumulative doses of corticosteroids than other SOT populations, such as kidney transplant (KT) recipients. In addition, UEA is a highly complicated surgical procedure that involves multiple tissues, including bone, and requires implantation of foreign material, thus exposing patients to deep infections in the early posttransplant period.

The aim of the present study was to assess the incidence and characteristics of infectious episodes after 20 years of experience in all patients who received UEA worldwide according to the International Registry on Hand and Composite Tissue Transplantation (IRHCTT). A matched cohort of KT recipients, who have the lowest rate of infections among the different SOT populations, was used as a comparison basis [27].

Patients and methods

Study type and data sources

We conducted an observational, multicenter, matched cohort study of all UEA recipients recorded in the IRHCTT and KT recipients of the French 'Données Informatisées et VAlidées en Transplantation' (DIVAT) transplant database. IRHCTT is a prospective collaborative registry including UEA and face transplant recipients worldwide, whose purpose is to collect detailed data on the characteristics and results of VCA [2]. The IRHCTT was founded in May 2002 and is supported by the International Society of Vascularized Composite Allotransplantation. For data quality control, information is systematically reviewed by the data manager (PP) at time of entry in the database and annually. The data manager evaluates the completeness of the registry and, if necessary, complementary information is requested from the transplant center. The DIVAT database is a prospectively maintained database including transplant and follow-up data of all adult kidney and/or pancreas transplant recipients of eight participating French transplant centers [28].

Patients

The study included all adult recipients of single or bilateral UEA performed between September 1998 and December 2016 reported to the IRHCTT and with a minimal follow-up of 60 days posttransplant as of February 22, 2017. UEA recipients who received simultaneous UEA and face allotransplantation or SOT before or after UEA were excluded. Each UEA recipient was matched with five recipients of a first KT from the DIVAT database, according to age (±5 years), sex, CMV serostatus of donor and recipient, type of induction immunosuppressive therapy (depleting or not depleting) and temporal proximity of the transplantation.

An appropriate written informed consent for data collection was obtained from all the participants at time of transplantation. The consent form contained information on the possibility of later anonymous use of the data for research purposes. Personal data are entered by each center in the system, which ensures security, privacy and

Transplant International 2019; 32: 693–701

confidentiality of the data. All the procedures are carried out in accordance with the ethical standards of the institutional review boards, national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data collection

Characteristics of the study population

Variables analyzed for the UEA and KT recipients included demographic data (age at time of transplantation, sex), transplant characteristics (donor and recipient pretransplant CMV serostatus, induction agent, immunosuppressive treatment at 3 months posttransplant), cause of amputation for UEA recipients, number of biopsy-proven or clinically presumed AR episodes that required a systemic treatment (i.e., by oral or parenteral corticosteroids and/or other, nontopical, immunosuppressants). After UEA, AR episodes were always proven by biopsy, information on AR episodes was systematically reviewed by the data manager (PP, an experienced transplant physician) at time of entry in the database and the revised Banff classification was used to standardize the definition of AR episodes [29]. If necessary, complementary information was requested from the transplant center. Patient and graft survival as well as cause of death were retrieved from the databases.

Infectious episodes

Both databases prospectively collect information about infections occurring after transplantation and requiring hospital management (outpatient or hospital treatment). Regarding UEA recipients, information on infections was systematically reviewed by the data manager (PP) and complementary information was requested from the transplant center if necessary. All infectious episodes reported to the two databases were retrieved and analyzed according to three posttransplant periods (early period, 0–6 months; intermediate period, 7–12 months; late period, >12 months), which are associated with different infectious risks in SOT recipients [30]. Infectious episodes were examined according to their nature (bacterial/viral/fungal/parasitic), the causal agent, the site of infection [graft's muscle or bone, graft's skin or subcutaneous tissues, skin or mucosa, pneumonia, urinary tract, catheter-related infection, infection of other sites (including isolated, noncatheter-related blood stream infections, ear, nose and throat infections, digestive infections), systemic viral infection] and their specific outcome. To distinguish persisting or relapsing infections from new infections, dates and agents of infectious episodes were analyzed.

Statistical analysis

Demographic variables were expressed as percentages. Quantitative continuous data were expressed as the mean ± standard deviation (SD). Descriptive data of demographic and transplant characteristics as well as infectious events were compared using the Mann–Whitney U test, the t-test, the χ^2 test or the Fisher's exact test, where appropriate.

To calculate the incidence rate of infections and AR episodes, we used the number of events as a numerator and as a denominator, the exact sum of days at risk for each UEA or KT recipient during the three periods of interest: from the day of transplantation to day+183 (early period), from day+184 to day+365 (intermediate period) and from day+366 to the end of follow-up (late period). Incidence rates were expressed as number of infections or AR episodes per 1000 transplant-days. Incidence rates of infectious events and AR episodes were compared using the mid-P test.

All analyses were based on two-sided P-values, with $P < 0.05$ considered statistically significant. Analyses were performed with GRAPHPAD PRISM, version 6.05 (GraphPad Software, Inc., San Diego, CA, USA).

Results

General characteristics of the study population

According to the IRHCTT, 64 patients underwent UEA worldwide between 1998 and 2016. Three of them were excluded from the study (history of kidney transplantation, $n = 2$; insufficient follow-up, $n = 1$). Forty (65.6%) received a bilateral and 21 (34.4%) a unilateral transplantation. The causes of amputation were explosion ($n = 17$, 27.9%), crush ($n = 15$, 24.6%), clean cut ($n = 10$, 16.4%), burn or electrocution ($n = 10$, 16.4%), sepsis ($n = 5$, 8.2%) or other ($n = 4$, 6.6%) (not shown). The 61 UEA recipients were matched with 305 KT recipients from the DIVAT database (Fig. 1). Baseline characteristics of the two groups are shown Table 1. The mean follow-up of UEA and KT recipients was 2583 ± 1876 and 2229 ± 1792 days, respectively ($P = 0.16$).

Immunosuppression regimens and acute rejection episodes

There was no difference between UEA and KT recipients in the composition of maintenance immunosuppression

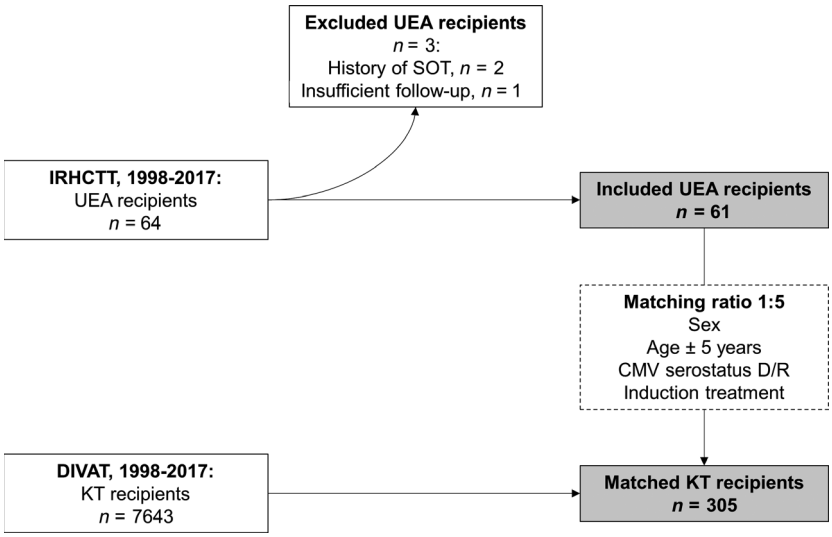

Figure 1 Flow-chart of patients included in the study. CMV, cytomegalovirus; D, donor; DIVAT, French transplant database of kidney transplant recipients; IRHCTT, International Registry on Hand and Composite Tissue Transplantation; KT, kidney transplantation; R, recipient; SOT, solid organ transplantation; UEA, upper extremity allotransplantation.

3 months after transplantation. During follow-up, the UEA recipients experienced a total of 79 AR episodes requiring systemic treatment, while the KT recipients cumulated 117 AR episodes requiring systemic treatment. As predictable, the incidence of AR episodes was significantly higher in UEA than in KT recipients during the early (4.02 vs. 1.33 AR episodes per 1000 transplant-days, $P < 0.001$) and the late periods (0.2 vs. 0.06 AR episodes per 1000 transplant-days, $P < 0.001$; Table 1).

Number and incidence of infectious episodes

During follow-up, the UEA and KT recipients cumulated a total of 61 and 243 infectious events, respectively. The mean number of infectious events per patient was 1 ± 1.4 and 0.8 ± 1.2, respectively ($P = 0.2$). Thirty-one (50.8%) UEA recipients and 129 (42.3%) KT recipients experienced one or more infectious events during follow-up ($P = 0.26$). Detailed numbers according to the post-transplant periods are given in Table 2. There was no significant difference in the proportion of UEA recipients with one or more infectious episodes according to the type of transplantation (proximal versus distal; unilateral versus bilateral; not shown).

During follow-up, the incidence rates of infectious events were 0.39 and 0.36 infectious episodes per 1000 transplant-days in UEA and KT recipients, respectively ($P = 0.57$, not shown). As previously reported in SOT recipients, the incidence rate of infectious episodes decreased over time after UEA (0–6 months: 3.27 per 1000 transplant-days; 7–12 months: 0.61 per 1000 transplant-days; >12 months: 0.15 per 1000 transplant-days). During the early period, the incidence rate of infectious episodes was significantly higher in UEA than in KT recipients (3.27 vs. 1.95 infectious episodes per 1000 transplant-days, $P = 0.01$). Thereafter, the infection incidence rates did not significantly differ between the two groups (Fig. 2).

Characteristics of infectious episodes

The causal agent was available for 65.6% ($n = 40$) of infectious episodes after UEA. The proportional distribution of infection sites is shown Fig. 3a. In all periods, nongraft localized mucocutaneous infections were the most frequent infections in UEA recipients, followed by allograft (skin, muscle or bone) and systemic viral infections (mostly CMV, 63.6%). However, during the late period, systemic viral infections were less frequent, while ear, nose and throat and gastrointestinal infections were more frequent. Isolated blood stream infections were rare after UEA (four out of 61 infectious episodes). With regard to mucocutaneous infectious episodes after UEA, early infections ($n = 10$) were caused by *Candida* spp. ($n = 3$), *Malassezia furfur* ($n = 1$), herpes simplex virus ($n = 1$), varicella zoster virus (VZV, $n = 1$) or by bacteria ($n = 4$), whereas late infections ($n = 6$) were caused by VZV ($n = 4$), herpes simplex virus ($n = 1$) or human papillomavirus ($n = 1$). As might be expected, urinary tract infections were more frequent during follow-up in KT recipients than in UEA recipients (30.9% vs. 8.2% of infectious events, $P = 0.002$). After 6 months

Table 1. Demographic and transplant characteristics of UEA and KT recipients.

	UEA (n = 61)	KT (n = 305)	P
Male sex	51 (83.6)	255 (83.6)	1
Age at time of transplantation (years, mean ± SD)	38.7 ± 12.7	38.7 ± 12.4	0.79
Induction agent*			
Anti-IL-2R	14 (25)	70 (23)	1
Thymoglobulin, alemtuzumab	42 (75)	210 (68.9)	
CMV serostatus†			
D+/R+	9 (16.7)	56 (18.4)	0.99
D+/R−	13 (24.1)	75 (24.6)	
D−/R+	14 (25.9)	74 (24.3)	
D−/R−	18 (33.3)	100 (32.5)	
Maintenance immunosuppression (M3)			
CNI	52 (94.5)	293 (96.1)	0.55
MMF/MPA	49 (90.7)	268 (87.9)	0.60
Prednisone	47 (88.7)	287 (94.1)	0.15
Sirolimus/everolimus	4 (8.3)	13 (4.3)	0.22
Incidence rate of AR episodes (AR episodes/1000 transplant-days)			
Early period (0–6 months)	4.02	1.33	<0.001
Intermediate period (7–12 months)	0.61	0.36	0.29
Late period (>12 months)	0.2	0.06	<0.001
All periods	0.5	0.17	<0.001
Follow-up (days, mean ± SD)	2583 ± 1876	2229 ± 1792	0.16

Data are No. (%) of patients, unless otherwise indicated. Missing data (UEA): *n = 5; †n = 7. Variables were compared using the t-test, the χ^2 test or the mid-P test, where appropriate.

AR: acute rejection; CMV: cytomegalovirus; CNI: calcineurin inhibitors; D: donor; KT: kidney transplantation; MMF/MPA: mycophenolate mofetil/mycophenolic acid; R: recipient; UEA: upper extremity allotransplantation.

Table 2. Number of infectious episodes after UEA and KT.

	UEA (n = 61)	KT (n = 305)	P
Number of infectious episodes	61	243	NA
0–6 months	35	98	
7–12 months	6	21	
>12 months	20	124	
Number of infectious episodes per patient, mean ± SD	1 ± 1.4	0.8 ± 1.2	0.2
0–6 months	0.6 ± 0.8	0.3 ± 0.7	0.002
7–12 months	0.1 ± 0.4	0.1 ± 0.3	0.9
>12 months	0.4 ± 0.9	0.5 ± 1	0.5
Patients with ≥1 infectious episode(s), n (%)	31 (50.8)	129 (42.3)	0.26
0–6 months	25 (41)	68 (22.3)	0.003
7–12 months	4 (7)	13 (4.9)	0.5
>12 months	13 (24.5)	48 (19.2)	0.5

Variables were compared using the Mann–Whitney U test or the Fisher's exact test, where appropriate.

KT: kidney transplantation; UEA: upper extremity allotransplantation.

posttransplant, pneumonia was rare in UEA recipients and more frequent in KT recipients (0% vs. 43% at the intermediate period, P = 0.07, and 5% vs. 28% at the late period, P = 0.03).

The origins of the infectious episodes (bacterial, viral, fungal, parasitic) according to the posttransplant period are shown Fig. 3b. In the UEA group, 37.7% (n = 23) of all infectious events were of viral origin. Early viral infections (n = 11) were predominantly caused by CMV (n = 6) while late viral infections (n = 9) were predominantly herpes zoster reactivations (n = 5, four of these five episodes occurred in the same patient). There was no BK virus

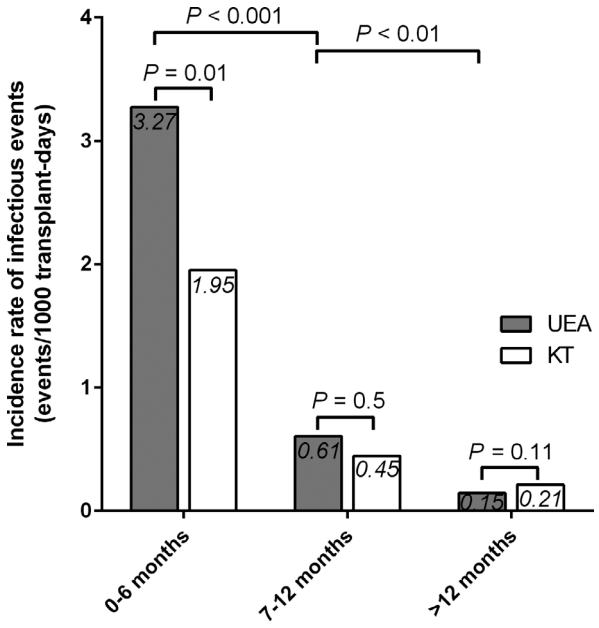

Figure 2 Incidence rates of infectious episodes during the early, intermediate and late posttransplant periods, after upper extremity allotransplantation and after kidney transplantation. Incidence rates of infectious episodes calculated as the [number of infectious events/(sum of transplant-days at risk)] for the early (0–6 months), intermediate (7–12 months) and late (>12 months) posttransplant periods and compared by the mid-P test. KT, kidney transplantation; UEA, upper extremity allotransplantation.

infection, no Human Herpesvirus-8 infection and one Human Papillomavirus infection reported (Table S1). With regard to CMV, seven UEA recipients presented eight episodes of CMV infection or disease. The CMV match of these seven patients was D+/R− in four cases (who all had CMV during the early period), D+/R+ in one case, D−/R− in two cases. No parasitic infection was recorded and one gastroenteritis during the late period was of unknown origin after UEA. During the early period, fungal infections were more frequent in UEA than in KT recipients (17% vs. 1% of infectious events, $P = 0.001$). After 6 months posttransplant, the proportional distribution of infection origins was significantly different between the groups: viruses were more often the cause of infections in UEA recipients as compared with KT recipients (50% vs. 14.3% at the intermediate period, $P = 0.10$, and 47.4% vs. 18.5% at the late period, $P = 0.02$) whereas bacteria were less often the cause of infections in UEA recipients as compared with KT recipients (33.3% vs. 85.7% at the intermediate period, $P = 0.02$, and 47.4% vs. 78.2% at the late period, $P = 0.005$).

Of note, the characteristics of infections in UEA recipients did not significantly differ between centers or periods during which the transplantation was performed (not shown).

Allograft and patient survival

Eight (13.1%) UEA recipients and 62 (20.3%) KT recipients lost their graft(s) during follow-up, not because of infection ($P = 0.22$). During follow-up, one (1.6%) UEA recipient and 20 (6.6%) KT recipients died ($P = 0.22$). The death of the UEA recipient was not because of infection while 3/20 (15%) KT recipients died from infection.

Discussion

After 20 years of experience, UEA has progressively emerged as an important option in the therapeutic arsenal of complex reconstructive surgery, offering hope to severely disabled patients for whom no other satisfactory replacement alternative is possible. From the beginning, the accurate evaluation of the risks of this highly specialized procedure has been hindered by the low number of patients. In the past 20 years, close to 100 patients have undergone UEA worldwide, now offering the possibility to perform more reliable studies. The IRHCTT is prospectively maintained by the large majority of the centers that have performed UEA (24 centers: 11 from Europe, six from USA, two from India, and one each from Australia, South Korea, Mexico, Taiwan, Turkey). This collaborative consortium has allowed us to provide herein the first systematic report of incidence and characteristics of infectious complications after UEA.

An important finding of this study was the high incidence of infection during the first 6 months post-UEA (3.27 per 1000 transplant-days), close to the incidence in the general population of SOT recipients during this period reported by San Juan *et al.* [27] (3.5 per 1000 transplant-days) and higher than in the study matched cohort of KT recipients (1.95 per 1000 transplant-days). The large majority (71.5%) of infectious syndromes during this period was attributed to nongraft localized mucocutaneous infections, systemic viral infections and graft localized infections. This raises important questions about anti-fungal, antiviral and anti-bacterial prevention during the early period post-transplantation and during any period when immunosuppression needs to be increased. This also highlights the possibility to improve our current practices in terms of prophylactic and/or preemptive anti-infectious treatments during these periods.

After the early period, the incidence of infectious episodes in UEA recipients declined dramatically to reach 0.15 per 1000 transplant-days after the first year posttransplant. This is below, or at least similar to the incidence of late infections in KT recipients (0.22 in the study

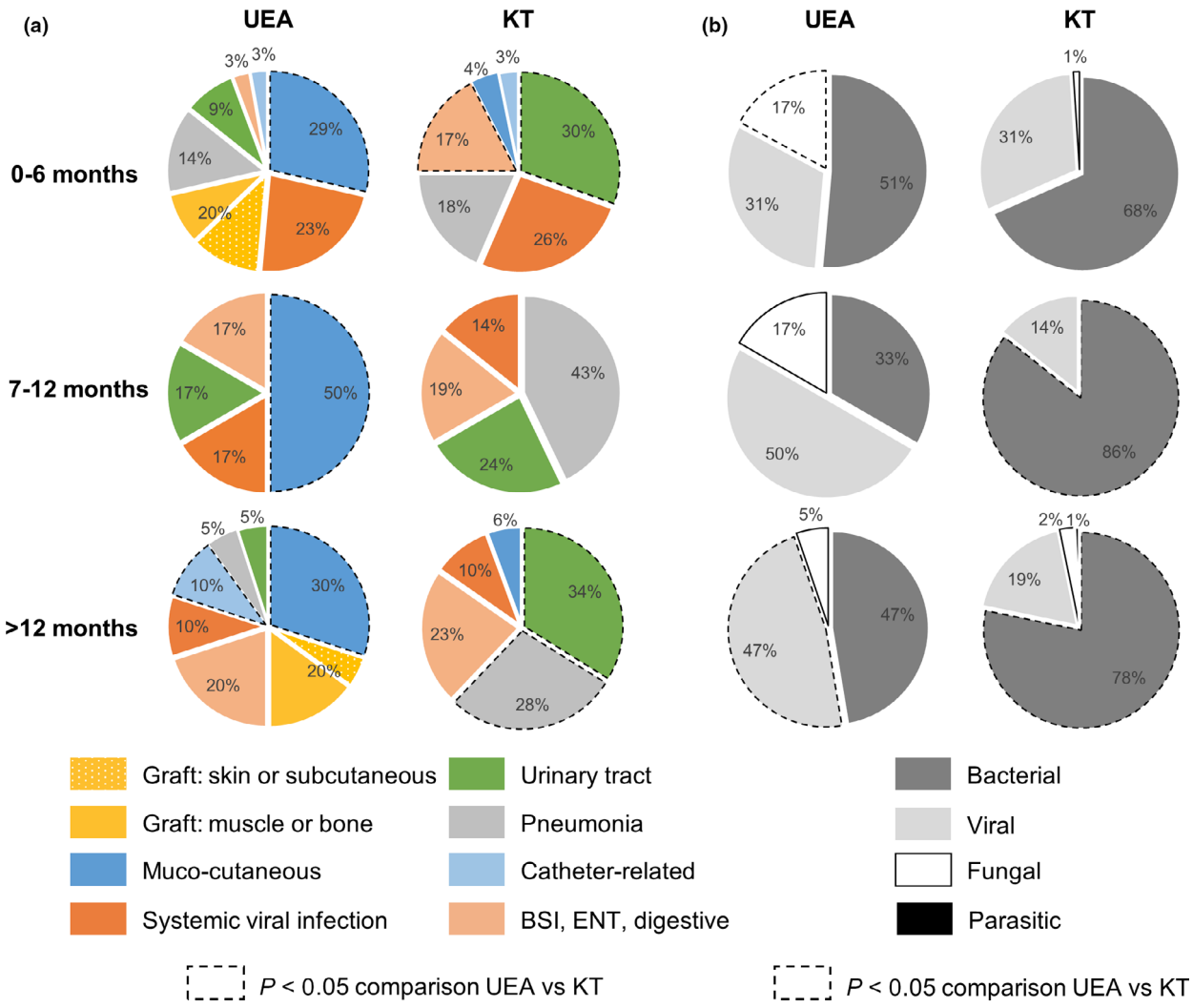

Figure 3 Distribution of sites (a) and origins (bacterial, viral, fungal, parasitic) (b) of infectious events during the early, intermediate and late posttransplant periods, after upper extremity allotransplantation and after kidney transplantation. The proportion of infectious episodes is indicated for each site of infection. Percentages may not total 100% because of rounding. Proportions were compared by the Fisher's exact test. BSI, blood stream infection; ENT, ear, nose, and throat; KT, kidney transplantation; UEA, upper extremity allotransplantation.

matched cohort and 0.28 per 1000 transplant-days in the study of San Juan *et al.* [27]), below the incidence of late infections in heart and liver recipients (0.34 and 0.31 per 1000 transplant-days, respectively [27]) and far below the incidence of late infections in pancreas and lung recipients (0.76 and 1.4 per 1000 transplant-days, respectively [27]). In addition, the infection pattern in UEA and matched KT recipients was different. There were significantly less bacterial infections and more viral infections (mostly CMV and VZV infections) in UEA recipients, less urinary tract infections and pneumonia and more muco-cutaneous infections, suggesting less severe infection episodes in UEA recipients. Importantly, no UEA recipient lost his graft or died from infection during the follow-up. Together, the low incidence, pattern and outcomes of late infections in UEA recipients suggest that the long-term burden of infectious complications is relatively low in this population. This may be one of the most important findings of the present study, since questions about the risk-to-benefit ratio of UEA are still raised and more data are needed by the transplantation community for a factual appreciation of this question.

CMV was the most frequent viral infection after UEA. While international guidelines recommend CMV prevention after SOT, CMV prevention and especially antiviral prophylaxis is not currently codified after UEA. Because the majority of CMV events occurred during the early period after UEA in D+/R− cases, this suggests a benefit of CMV prophylaxis at least during the first 6 months after UEA in D+/R− cases. However, data on antiviral prophylaxis after UEA were not available for this study, precluding definite conclusions.

The present study has some limitations. Detailed data about prophylactic strategies and isolated microorganisms for each infection episodes are missing, as these items are not included in the database. The evaluation of infection was based on the appreciation of transplant physicians as per centers' practice and the variability between definitions could not be verified retrospectively. Another limitation comes from the long period covered by this study. In 20 years, the management of transplanted patients has evolved, particularly regarding the use of immunosuppressive drugs and regarding prophylactic or preemptive anti-infectious strategies. It is likely that the medical management of patients transplanted more than 15 years ago is significantly different from that of patients transplanted more recently. Of note, we did not find any significant difference regarding the pattern of infectious complications according to the period during which the UEA was performed. Finally, the revised Banff classification was used to standardize the definition of rejection episodes even though this classification remains controversial in UEA recipients.

It is also important to note that this study did not include face transplant recipients. In the context of infectious diseases, we felt that face transplantation had to be distinguished from UEA because of the peculiarity and complexity of this procedure that involves mucosal tissues prone to be colonized by various pathogens and associated with a particularly high risk of infection of the surgical site [8,23,31,32].

In conclusion, this first systematic report of infectious complications after UEA reveals that the incidence of infection is high during the first 6 months posttransplant, which emphasizes the necessity to carefully define the optimal prophylactic and/or preemptive strategies during this period. After 1 year, the incidence of infection is low, with favorable patterns and outcomes. This is important information for a precise assessment of the risk-to-benefit ratio of UEA.

Conflict of interest

The authors of this manuscript have no conflict of interest to disclose as described by *Transplant International*.

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Authors' contributions

AC, PP, EM, and AS contributed to the conception and to the design of the study and drafted the manuscript. AC and PP contributed to the data acquisition. AC performed the statistical analysis. AC, EM, and AS contributed to the data interpretation. AC, PP, JK, AG, LB, OT, PV, FB, EM, and AS participated in editing the paper for important intellectual content, correction and approval of the final version.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Infectious episodes of viral origin after UEA.

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