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High mortality and graft loss after infective endocarditis in kidney transplant recipients: a case-controlled study from two centers

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Abstract

Purpose

Kidney Transplant Recipients (KTRs) tend to develop infections with characteristic epidemiology, presentation and outcome. While infective endocarditis (IE) is among such complications in KTRs, literature is scarce. We describe the presentation, epidemiology, and factors associated with IE in KTRs.

Methods

We performed a retrospective case/control study which included patients from two centers. First episodes of definite or possible IE (Duke criteria), in adult KTRs from January 2007 to December 2018 were included, as well as two controls per case, and followed until December 31 2019. Clinical, biological, and microbiological data and the outcome were collected. Survival was studied using the Kaplan-Meier method. Finally, we searched for factors associated with the onset of IE in KTRs by the comparison of cases and controls.

Results

Seventeen cases and 34 controls were included. IE was diagnosed after a mean delay of 78 months after KT, mostly on native valves of the left heart only. Pathogens of digestive origin were most frequently involved (six *Enterococcus spp,* three *Streptococcus gallolyticus* and one *Escherichia coli*), followed by *Staphylococci* (three cases of *S. aureus* and *S. epidermidis* each). Among the risk factors evaluated only age was significantly associated with the occurrence of IE in our study (63.8 years for cases vs. 55.6 years for controls, P=0.03)

Patient and death-censored graft survival were greatly diminished five years after IE compared to controls being 50.3% vs. 80.6% (p<0.003) and 29.7% vs. 87.5% (p<0.002), respectively.

Conclusion

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IE in KTRs is a disease that carries significant risks both for the survival of the patient and the transplant.

Keywords: Infective endocarditis; Kidney Transplantation; Survival analysis; graft failure; transplant infectious diseases

Funding

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Conflicts of interest/Competing interests

The authors declare no competing interests or conflict of interests in this study.

Availability of data and material

The data and material are available upon request to the corresponding author.

Code availability

Not applicable

Authors' contributions

YT, CD designed the study, collected and analyzed the data and wrote the article. JT designed the study, analyzed the data and wrote and reviewed the article. PR performed the database extraction of the data. BB, AA, ME, JFF and ZE reviewed the article.

Ethics approval / Consent for publication

All patients provided consent to be included in the local databases before their transplantation, and granted us with the authorization to anonymously use their clinical data in the perspective of clinical research. The clinical databases were approved by the French Ethics Committee on the Treatment of Computerized Data in the Field of Medical Research, under the auspices of the French Ministry of

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Research (declaration number: 2097646 v 0 for Pitié-Salpêtrière Hospital and 2210609609.v.0 for Limoges Hospital).

Consent to participate

Non applicable.

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Introduction

Infective Endocarditis (IE) is an invasive infection characterized by high inoculum of a pathogen that has a strong propensity to form biofilms, and that is also capable of systemic dissemination. Worldwide, this severe disease (with 30% 1-year mortality) remains rare. Over the last decades a trend was observed with an increase in staphylococcal infections and increasing incidence in older patients with more comorbidities[1].

End-Stage Renal Disease (ESRD) is a growing worldwide concern, with almost one million ESRD patients in the United States in 2019[2], mostly elderly patients with comorbidities. IE in ESRD patients has already been described in chronic hemodialysis (HD) patients, where it may be a consequence of a staphylococcus bacteriemia, a very common condition in this patient subgroup exposed to dialysis fistula puncture or central catheter usage three times a week. Solid Organ Transplant Recipients (SOTRs) undergo immunosuppressive treatment to prevent graft rejection, and as a result they are susceptible to more frequent, more severe and atypical infections[3]. IE in this population is not well described in the literature apart from uncommon and isolated cases.

We therefore sought to describe the presentation, epidemiology, risk factors and outcome of IE in Kidney Transplant Recipients (KTRs) through a case/control study.

Material and Methods

Study Design, Setting, and Participants

We performed a retrospective case-control study with patients from two centers: the Pitié-Salpêtrière (Assistance Publique - Hôpitaux de Paris, France) and in the Dupuytren (Limoges, France) Hospitals. Cases were screened from the databases of the medical-based information systems in the two hospitals. Patients were included according to the following conditions: kidney transplant recipients with a functioning allograft, diagnosed for a first episode of certain or possible IE, on a native heart (exclusion of kidney-heart recipients), between January 2010 and December 2019. Two

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controls were included with each case; these were the patients who had received a kidney transplant just before and just after the case in the same center, provided that those patients survived at least until the delay of IE in the case. If one of the following exclusion criteria applied to the controls, the next-previous or the next-after transplanted patient was included instead: diagnosis of IE during the study period (included as a case), death before the diagnosis of the IE in the corresponding case, or presence of another organ transplanted with the kidney.

Clinical data and definitions

The diagnosis of IE was made according to the modified DUKE criteria[1,4]:

- Definite IE: 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria
- Possible IE: 1 major and 1 minor or 3 minor criteria

The onset date of the episode was defined by the start of antibiotic therapy for IE. The following clinical data were collected from the medical record:

- Medical history: presence of a heart disease at high risk of IE heart (prosthetic valves, congenital cyanotic heart disease, or history of infective endocarditis), a history intravenous drug use, pre-transplant diabetes or new onset diabetes after transplantation (NODAT)

- Kidney Transplantation (KT) history: the most recent estimated glomerular filtration rate (eGFR, MDRD formula) considered as stable before IE onset, induction and maintenance immunosuppressive treatments before and at the time of the infectious episode, the presence of high levels of calcineurin inhibitors or antimetabolites prior to the infectious episode (trough level > 10ng/mL for tacrolimus or > 150 ng/mL for cyclosporine, mycophenolate mofetil area under the curve (MMF AUC) > 60mg.h/L), the treated episodes of rejection and viral infections (BK virus and cytomegalovirus, CMV) between transplantation and the IE episode.

- The characteristics of the IE with the time to onset after KT, bacteriological documentation, infectious gateway, ultrasonography features, type of valve, vascular (embolization, intracranial

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hemorrhages, mycotic aneurysms) and immunological (glomerulonephritis) complications, and the presence of an indication for surgery according to the European Society of Cardiology[5],

- IE therapeutic management: antibiotic therapy used, treatment duration and surgical management

- Outcome: Patient and renal graft survival and eGFR one year after the IE were collected. For controls, the delay between the IE diagnosis in the corresponding case and the event (death, loss of graft function, loss to follow-up, or end of the study) was considered for the survival analysis. The end of the study was December 31, 2019.

Statistical analysis

The statistical analyses were performed using GraphPad PRISM®. The annual incidence was estimated by dividing the annual number of cases of IE by the number of living KTRs in the two centers during the same year. Quantitative variables are presented as mean ± standard deviation or median (inter-quartile range, IQR) according to their normal or skewed distributions. Comparisons were made using the Student t test. Qualitative variables are presented as numbers (percentages). The data were compared using the Fischer or Chi2 test. Survival analyses were performed using the Kaplan-Meier method. A Log-rank test was performed for the comparison between the two groups, with a p value < 0.05.

Ethics

All patients provided consent to be included in the local databases before their transplantation, and granted us the authorization to anonymously use their clinical data in the perspective of clinical research. The clinical databases were approved by the French Ethics Committee on the Treatment of Computerized Data in the Field of Medical Research, under the auspices of the French Ministry of Research (declaration number: 2097646.v.0 for Pitié-Salpêtrière Hospital and 2210609609.v.0 for Limoges Hospital).

Results

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Population and incidence of IE

Over the study period 17 KTRs were diagnosed with IE, resulting in a mean annual incidence of 1.1‰. We identified and included 34 controls. The characteristics of the population are shown in Table 1. IE occurred mostly in men (sex ratio 2:1), after a mean delay of 77.8±82.3 months after KT. However, men predominated among KT controls, and the incidence of IE was not sex-related. The mean age at IE diagnosis was 63.8±13 years, and cases were older than controls (55.6±12 years, P=0.03). All cases were recipients of a first kidney transplant. The repartition of the initial nephropathy also differed between cases and controls (p<0.01). There were more vascular nephropathies in cases and more undetermined nephropathies in controls.

	Cases (n=17)	**Controls (n=34)**	**P value**
	n (%) or mean±SD	n (%) or mean±SD	
Age (years)	63.8±13.4	55.6±11.7	**0.03**
Sex (male)	11 (66.6)	19 (55.9)	0.54
First transplantation	17 (100)	30 (88.2)	0.29
Time for onset after KT (months)	77.8±82.3	NA	1
eGFR at diagnosis (ml/min/1.73 m²)	43.6±21.9	52.3±24.0	
Diabetes	7 (41)	7 (20.6)	0.2
After transplant	3 (17.5)	4 (11.8)	
Pre-existing	4 (23.5)	3 (8.8)	
Initial nephropathy			**<0.01**
Vascular/Hypertension	5 (29.4)	2 (5.9)	
Diabetes	3 (17.6)	5 (14.7)	
PKD	3 (17.6)	4 (11.7)	
IgA	2 (11.8)	2 (5.9)	

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Glomerulonephritis	2 (11.8)	3 (8.8)
aHUS	2 (11.8)	0
Undetermined	0	7 (20.6)
Other	0	11 (32.4)

eGFR: estimated Glomerular Filtration Rate; NA: not applicable

Table 1: Characteristics of the patients

Clinical presentation and microbiological epidemiology of IE

The clinical presentation and management of the cases of IE are summarized in Table 2. All cases were left heart endocarditis, and only 3 occurred on prosthetic valves. Mitral and aortic valves were equally involved.

The bacteria causing the infection were: *Enterococcus spp* (6), *Streptococcus gallolyticus* (3), coagulase-negative *Staphylococci* (CNS; 3), *Staphylococcus aureus* (3), *Escherichia coli* (1) and one undocumented case. Concerning IE on prosthetic valves (one mechanical and two bioprosthetic valves), *Streptococcus gallolyticus*, *Enterococcus faecalis* and *Staphylococcus epidermidis* were found (one of each). One patient with a bioprosthetic valve had a definite *Staphylococcus epidermidis* IE, followed 10 months later by a new episode with *Escherichia coli* (not included in the analysis). The microorganisms were considered to be of digestive origin in 10 cases and of cutaneous origin in 6 cases. There was no case of IE with an oral origin.

Vascular embolism was observed in six subjects. No immunological complications were found.

Seven patients presented with an indication for surgery as recommended by the European Society of Cardiology in 2015[5] (two abscesses, two severe regurgitations and three vegetations > 15mm), three underwent surgery (one with severe aortic and mitral regurgitations and two with a vegetation > 20mm).

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The duration of the antibiotic therapy was six weeks, except for one case who received only four weeks of gentamicin and daptomycin for a methicillin-resistant *S. aureus* uncomplicated endocarditis of a native valve. Aminoglycosides were used in 12 patients (4 with Staphylococcal IE, 3 with Enterococcal IE, 3 with Streptococcal IE, and 1 with *E. coli* IE and in the undocumented case). Vancomycin was used in 3 patients (one case of *Enterococcus faecium*, methicillin-resistant *Staphylcococcus epidermidis* and *Staphylococcus aureus* each).

Characteristics	**N=17,** n (%) unless otherwise specified
Definite IE	12 (70.6)
Possible IE	5 (29.4)
Valve	
Native	14 (82.4)
Prosthetic	3 (17.6)
Aortic IE	5 (39.4)
Mitral IE	7 (41.2)
Mitral and aortic	4 (23.5)
Echocardiography data	
No vegetation	2 (11.8)
Ring abscess and/or severe valve leakage	6 (35.3)
Vascular complications	6 (36.3)
Microbiology	
Enterococci	6 (35.3)
Streptococcus gallolyticus	3 (17.6)
Staphylococcus aureus	3 (17.6)

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Coagulase-negative Staphylococci	3 (17.6)
Escherichia coli	1 (5.9)
No documentation	1 (5.9)
Probable origin of the causative bacterium	
Digestive	10 (58.8)
Cutaneous	7 (41.2)
Unknown	1 (5.9)
Treatment	
Antibiotic treatment duration (weeks), mean±SD	5.9±0.5
Aminoglycoside use	12 (70.6)
Indication for surgery	7 (41.2)
Surgery	3 (17.6)

Table 1: Clinical, radiological and microbiological characteristics of IE in KTRs

Analysis of risk factors

In order to identify risk factors for IE, the distribution of clinical characteristics (Table 1) and comorbidities and IS protocols (Table 3) were compared between cases and controls. Only age and the initial nephropathy were significantly different. Cases were significantly older than controls (63.8±13 vs. 55.6±12 years, p=0.03, Table1) and cases suffered more frequently from a vascular nephropathy than cases (29.4 % vs. 5.9%).

The comorbidities known as potential risk factors were not differently distributed between cases and controls. IS protocols were also evenly distributed; only high trough levels of CNI tended to be observed more frequently in cases than in controls (p=0.08; Table 3).

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		Cases (N=17), n (%)	Controls (N=34), n (%)	P value
Comorbidities				
Intravenous drug use		0 (0)	0 (0)	1
Heart prosthetic valve		3 (17.6)	2 (5.9)	0.32
Pre-transplant diabetes		4 (23.5)	4 (11.8)	0.21
NODAT		3 (23.1)	3 (10)	0.35
CMV infection		9 (52.9)	11 (31.4)	0.26
BK virus infection		1 (5.9)	8 (23.5)	0.24
Treatment of acute rejection		2 (11.8)	3 (8.8)	1
Immunosuppressive treatment				
Induction therapy	ATG	13 (76.5)	24 (70.5)	1
	Basiliximab	4 (23.5)	10 (29.5)	1
Maintenance therapy	Steroids	15 (88.2)	29 (85.3)	1
	MMF	16 (94.1)	30 (88.8)	0.65
	CNI	17 (100)	34 (100)	1
	Other	1 (5.9)	3 (8.8)	1
Drug monitoring				
AUC MMF >60 mg.h/L		1/6 (16)	0/10 (0)	0.36
Elevated anti-calcineurine trough level*		5/14 (37.5)	2/22 (9.1)	0.08

AUC: Area under the curve; MMF: mycophenolate mofetil. CMV: Cytomegalovirus; ATG: Anti-Thymocyte globulin, *: >10 ng/mL for tacrolimus and 150 ng/mL for ciclosporin

Table 3: Comparison of risk factors for IE between cases and controls. These factors were compared in addition to the initial characteristics which are compared in Table 1.

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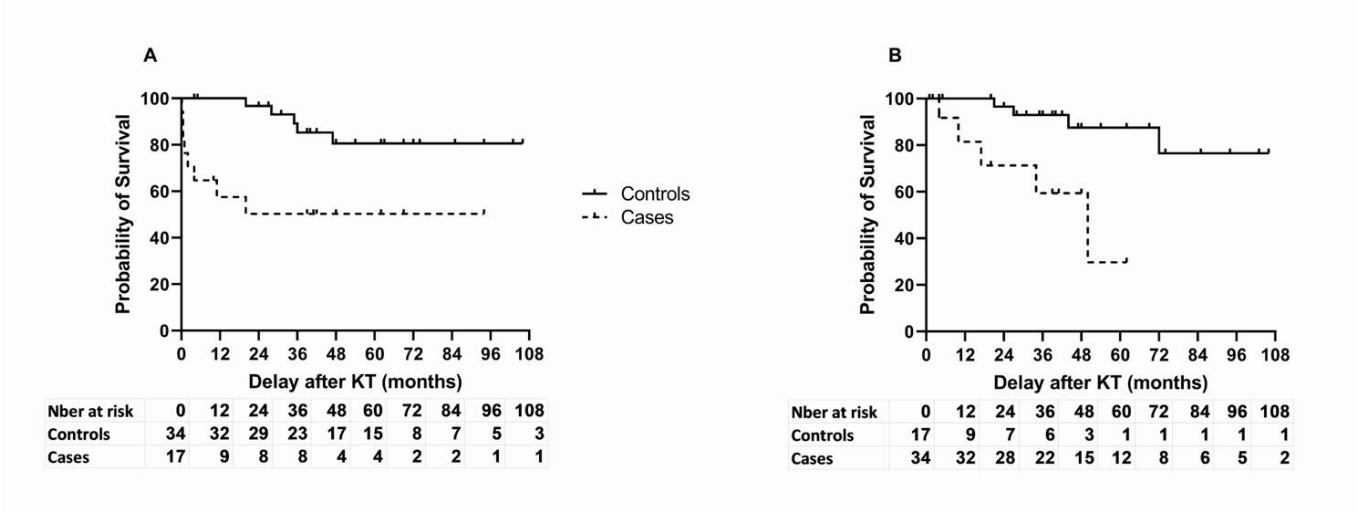
Patient and graft survival

Patient survival was greatly diminished after an episode of IE (Figure 1A). One- and 5-year survivals were 58 [31 – 77] vs. 100 and 50 [24 – 72] vs. 80.6 [59 – 92] for cases and controls, respectively ($p<0.003$). The median survival was 20 months for cases and was not reached in controls at the end of the study. Seven patients with IE died within the first year of follow-up including 5 of them within the first 6 months.

Death-censored graft survival was also greatly lower in cases than in controls (Figure 1B). The estimated graft survival at one and five years was 81.5 [44 – 95] months vs. 100 and 29.7 [1.6 – 70] vs. 87.5 [65– 96] for cases and controls respectively ($p<0.002$). The median graft survival for cases was 49 months and not reached at the end of follow-up for controls.



Nber at risk	0	12	24	36	48	60	72	84	96	108
Controls	34	32	29	23	17	15	8	7	5	3
Cases	17	9	8	8	4	4	2	2	1	1

Nber at risk	0	12	24	36	48	60	72	84	96	108
Controls	17	9	7	6	3	1	1	1	1	1
Cases	34	32	28	22	15	12	8	6	5	2

Figure 1: Patient (A) and death-censored graft (B) survival. Cases (dotted line) and controls (solid line) survival were estimated according to the Kaplan Meier's method.

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Discussion

IE is well described in the general population[1,6,7]. There are also numerous reports in hemodialysis (HD) patients, where IE is reported as both frequent and deadly, with a 45.6% mortality [8][9]. This is probably due to the frequent vascular punctures in these patients, which represents the most common infectious gateway[8,9].

In our study, the annual incidence is possibly lower (1.1‰) than in HD patients (1.7-2‰)[10,11]. This remains surprisingly high if we consider that none of the patients in our study harbored a central venous device nor underwent repeated vascular puncture as a risk factor. The annual incidence of IE in KTRs was higher than in the general population in Western countries (40 cases per million people) [12,13]. This is probably the consequence of the IS treatment and of the comorbidities of this population.

IE in KTRs occurred mostly in younger people than in the general population[1,6,7,11], and on hearts without any IE-predisposing conditions, as in the general population[14]. In our series, IE only occurred on left heart valves, but right heart valve IE has also been reported in KTRs previously[14].

The microbiology also appears different from what has been described in HD patients, where there is a large predominance of *Staphylococci* [8,9]. In that respect the epidemiology in our study is closer to that of the general population[1]. We found that digestive bacteria predominate, with *Enterococci* as the most frequent pathogen as previously described in SOTRs [15–21,14,21]. A hypothetical mechanism, in the absence of an identified digestive gateway (colonoscopy was performed in most of the cases where a digestive bacterium was identified, even though we did not collect the results of this exam in our study), could be the alteration of the gut microbiota by the combination of antibiotic treatment frequently used after transplantation, and of immunosuppressive drugs. The changes in the gut flora after transplantation often include an increase in proteobacteria, and an increase in the Firmicutes/Bacteroidetes ratio [22–24]. This dysbiosis has been associated with the development of infections due to immune dysregulation and/or the promotion of virulent strains [3,25].

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In contrast with what has been reported for SOTRs in one study[21,26] but consistent with what was found in another[21] we found no case of fungal endocarditis. The undocumented cases in our study survived for more than seven years after an empiric antibiotic treatment, making a fungal origin of the infection very unlikely.

The time to onset after transplantation was consistent with other reports for KTRs, with a mean delay of 3 to 5 years [21,27].

Only age and vascular nephropathy were associated with IE in our study, as already reported[1]. Other specific triggering factors remain unknown.

A history of CMV infection was not found to be associated with IE, as opposed to earlier studies where co-occurring CMV replication was found to be associated with both disease and mortality [20,28], suggesting that CMV infection is a hallmark of profound immunosuppression.

We found IE is a frequently deadly disease, with a one-year mortality of 43%, when all the controls survived after the same delay. This mortality appears comparable with what has previously been described in SOTRs[17,20], and in HD patients [17,20] but is much higher than what has been described in the general population [7]. This enhanced severity could reflect the frailty of immuno-compromised hosts but could also be related to the virulence of the pathogens, or favored by the gut microbiota dysbiosis as mentioned above. Inadequate treatment, due to imprecise GFR estimation tools in KTRs [29] and under- or over-dosing in the anti-infectious therapy could also contribute to this poor outcome. Importantly, only three of the seven patients with a consensual surgical indication actually received surgery.

More than 70% of the patients received aminoglycosides. According to the 2015 ESC Guidelines[5], the remaining indications for aminoglycoside are Enterococcal IE, some Streptococcal IE (two weeks of a gentamycin-based regimen in young patients with normal renal function) and IE without microbiological documentation[5]. Only 41% of the aminoglycoside prescriptions in our study match

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one of these indications. The overuse of aminoglycoside can probably be explained by the fact that most of the cases were included before 2015.

Finally, death-censored graft survival after IE also appeared unexpectedly low, with half of the grafts lost after four years, versus 13% in the controls after the same delay. Endocarditis is known to result in acute and long-term kidney complications[30] due to infectious, post-infectious, immunological or drug-related mechanisms. Our study was not designed to explore the cause of renal failure in the patients who were included. Antibiotic-related renal toxicity (70% of the patients received either vancomycin or aminoglycosides therapy) or immunosuppression modulation following the episode may have participated to this poor prognosis. The potential consequences of nephrotoxic drugs on long term kidney function should particularly be considered when taking decisions in antibiotic treatments in this specific setting.

The incidence of IE after kidney transplantation is higher than in the general population but lower than in hemodialysis patients. It is a critical disease, both for the patient and the transplant function. Bacteria from the gut microbiota are overly represented, which underlines the fact that the host-pathogen crosstalk is insufficiently understood and should be further investigated in KTRs.

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