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Epidemiology and risk factors of multiple opportunistic infections after kidney transplantation: a prospective multicentric study

Romain Gueneau

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Année 2020

Epidémiologie et facteurs associés aux infections opportunistes multiples après transplantation rénale : Etude prospective multicentrique

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Par Romain GUENEAU

[Données à caractère personnel]

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LISTE DES ABREVIATIONS

ATG : anti-thymoglobulin

BMI : body mass index

BLSE : beta-lactamase à spectre élargis

CHU : centre hospitalo-universitaire

CI : confidence interval

CMV : cytomégalovirus

DIVAT : Données Informatisées et VALides en Transplantation

ECD: Extended Criteria Donor

HBP: high blood pressure

HEV: E hepatitis virus

HLA: human leukocyte antigen

JCV: JC virus

KTR: kidney transplant recipients

OR: odds-ratio

PRA: panel reactive antibody

SCD: Standard Criteria Donor

SD: standard deviation

SOT: Solid organ transplantation

VZV: Varicella zoster virus

RESUME

Introduction

Le risque infectieux est fortement augmenté après transplantation rénale. Les infections représentent la seconde cause de mortalité après les maladies cardiovasculaires et pourraient être associées à la perte de fonction du greffon. Parmi elles, les infections opportunistes (IO) sont une complication non négligeable malgré les surveillances et prophylaxies mises en place. Des facteurs de risque spécifiques à chaque pathogène opportuniste ont été identifiés par le passé, mais de façon générale les facteurs de risque d'IO sont peu étudiés, et aucune étude ne s'est intéressée aux patients ayant de multiples IO. L'objectif de ce travail était de décrire les IO, en particulier multiples, après transplantation rénale, et d'en étudier les facteurs de risque.

Matériels et méthodes

Nous avons inclus prospectivement les patients adultes ayant reçu une transplantation rénale entre janvier 1998 et décembre 2015 dans 6 centres français de la cohorte DIVAT. Tout patient présentant au moins 2 IO a été considéré comme « IO multiple ». Les IO ont été détaillées, et les facteurs associés à la récurrence ont été analysés en utilisant un modèle proportionnel de Cox temps-dépendant.

Résultats

Parmi les 9541 patients inclus, 1872 patients ont présenté au moins une IO (19.6%), et 334 (17.8%) en ont en présenté deux ou plus, soit un total de 2292 IO. La maladie à CMV ($n=550$) était l'IO la plus fréquente, suivie de VZV ($n=531$), la néphrite à BKV ($n=200$), et les diarrhées à *Clostridium difficile* ($n=173$) et *Norovirus* ($n=160$). En analyses multivariées, les facteurs associés à la survenue d'IO multiples étaient l'âge (HR/10 ans: 1.21 (1.11 – 1.33), $p<0.001$), le sexe féminin (HR 1.37 (1.08 – 1.74)), $p=0.009$), la dénutrition (HR BMI $<17\text{kg/m}^2$: 2,27 (1,18 - 4,38)), la diminution du débit de filtration glomérulaire (HR/ 10ml/min DFG: 1.14 (1.05–1.22), $p=0.001$), un antécédent de tuberculose avant la transplantation (HR 2.13 (1.03 – 4.39), $p=0.02$), une première IO par *Clostridium difficile* (HR 1.70 (1.19 – 2.43), $p=0.004$), et la survenue de cytopénie (HR 1.30 (1.02 – 1.65), $p=0.035$) ou thrombose (HR 1.47 (1.13 -1.93), $p=0.005$) après transplantation. Le surpoids et l'obésité étaient associés à moins de récurrences (HR 25-30 kg/m^2 : 0.73 (0.55 – 0.97); HR $>30\text{kg/m}^2$: 0.50 (0.33 - 0.76)), de même qu'une première infection opportuniste par VZV (HR 0.68 (0.48 – 0.92), $p=0.009$).

Conclusion

Après transplantation rénale, les IO sont fréquentes, essentiellement virales, et 17.8% des patients présentent au moins une autre IO après la première. Les facteurs de risque associés à la récurrence sont l'âge, le sexe féminin, la baisse du DFG, la dénutrition, et la survenue de cytopénie ou thrombose post transplantation. *Clostridium difficile* est le seul pathogène associé à une augmentation du risque de récurrence. D'autres études sont nécessaires pour adapter le suivi et les prophylaxies après une première infection opportuniste.

SUMMARY

Introduction

Kidney transplant recipients (KTR) are at increased risk of infections. Infections are the second cause of mortality after KT, and are reported to be associated with graft dysfunction and loss. Opportunistic infections (OI) also represent an important burden after kidney transplantation, despite prophylaxis and prevention programs. Specific risk factors have been identified per pathogen, but few data exist regarding global OI risk factors. Also, there is no data on risk factors for multiple OI in KTR. Thus, the aim of our study was to describe opportunistic infections, especially multiple OI, and to determinate the factors associated with multiple OI in KTR.

Materials and methods

We prospectively included all KTR between January 1998 and December 2015 in six French centers (Lyon, Montpellier, Nancy, Nantes, Necker, and Toulouse) participating to DIVAT cohort. Patients were considered to present multiple OI if they presented at least two OI. Factors associated with the recurrence of an OI were analysed using a time varying Cox proportional model.

Results

Among the 9541 patients included, 1872 presented an OI (19.6%), and 334 of them (17.8%) presented more than one OI representing a total of 2292 OI. *CMV* disease (n=550) was the most frequent OI followed by *VZV* (n=531), *BKV* nephritis (n=200 p), *Clostridioides difficile* (n=173) and *Norovirus* (n=160) diarrheas. In multivariate analysis, factors associated with OI recurrence were age (HR per 10 years increase: 1.21 (1.11-1.33), p<0.001), female gender (HR 1.37 (1.08- 1.74)), p=0.009), denutrition (HR BMI<17kg/m² : 2.27 (1.18- 4.38)), decreased renal function (HR per 10ml GFR decrease: 1.14 (1.05 ; 1.22), p=0.001), an history of tuberculosis pre-transplantation (HR 2.13 (1.03 ; 4.39), p=0.02), *Clostridioides difficile* colitis as the first OI (HR 1.70 (1.19- 2.43), p=0.004), and cytopenia (HR 1.30 (1.02- 1.65), p=0.035) and thrombosis (HR 1.47 (1.13- 1.93), p=0.005) post transplantation. Overweight and obesity were associated with less recurrence (HR 25-30 kg/m²: 0.73 (0.55- 0.97); HR >30kg/m²: 0.50 (0.33 ; 0.76)) as was *VZV* as the first OI (HR 0.68 (0.48- 0.92), p=0.009).

Conclusion

In KTR, OI are frequent, mostly viral, and 17.8% of patients with OI develop a recurrence. Factors associated with multiple OI are age, female gender, lower GFR, denutrition, as well as post-transplant cytopenia or thrombosis. *Clostridioides difficile* is the only pathogen associated with an increase of recurrence. Further studies are required to adjust prevention and follow-up programs after a first opportunistic infection.

EPIDEMIOLOGIE DE L'INSUFFISANCE RENALE EN FRANCE

1. L'insuffisance rénale terminale en France

En 2018, selon les données du registre REIN, 89692 patients bénéficiaient d'un traitement de suppléance de l'insuffisance rénale chronique terminale soit une prévalence de 1328 patients par million d'habitants. Parmi ces patients, 49271 (54.9%) étaient en dialyse (dont 6% en dialyse péritonéale) contre 40271 porteurs d'un greffon rénal fonctionnel (12% ayant reçu un greffon d'un donneur vivant apparenté). En 2018, 11 343 nouveaux patients ont bénéficié d'une suppléance rénale de novo, soit une incidence de 168 patients/million d'habitants. Parmi ces patients, les principales étiologies de la maladie rénale étaient par ordre décroissant : la néphropathie hypertensive (25.1%), la néphropathie diabétique (21.5%), la glomérulonéphrite primitive (10.3%), les néphropathies interstitielles (6.5%), la polykystose rénale (5.5%), les néphropathies génétiques (0.8%) et l'étiologie était indéterminée chez 17% des patients. En France, en 2018, 3567 greffes rénales ont été réalisées, parmi lesquelles 15% à partir de donneurs vivants apparentés et 13% de manière préemptive. Le taux de mortalité moyen était de 9.8% pour l'ensemble de la population bénéficiant d'une épuration extra-rénale, avec des différences entre les deux groupes : 15.9% des personnes dialysées contre 2.4% chez les personnes transplantées. Cette différence est expliquée par le sur-risque de morbi-mortalité associé aux techniques de dialyse comparativement à la transplantation, mais aussi par la différence d'âge et de comorbidités entre les deux populations, les patients transplantés ayant en médiane 58 ans contre 71 ans chez les patients dialysés (1).

2. Epidémiologie des infections

Les infections représentent une part importante de la morbi-mortalité chez les patients transplantés d'organe et notamment chez les personnes transplantées de rein. Dans une cohorte nationale finlandaise incluant 3249 patients ayant reçu une transplantation rénale entre 1990 et 2012, les maladies infectieuses représentaient 21% de l'ensemble des causes de décès, et étaient la 2ème cause mortalité, après les maladies cardiovasculaires. L'incidence différait entre les deux périodes de l'étude avec 9.1 puis 4.6 décès pour 1000 patients/année sur les périodes 1990-1999 et 2000-2012 respectivement. Les facteurs associés au décès par maladie infectieuse étaient l'âge, la période 1990-1999, la néphropathie diabétique et un délai de dialyse pré-transplantation supérieur à 12 mois. L'infection la plus fréquemment associée au décès était la pneumonie, mais la documentation microbiologique n'était pas disponible(2). De même en France, sur la période 2002-2018, les maladies infectieuses étaient la deuxième cause mortalité chez les patients en insuffisance rénale terminale après les maladies cardiovasculaires avec 8729 décès, représentant 12.8% des décès(1).

RESISTRA est une cohorte nationale espagnole qui a pour but de décrire et d'analyser l'incidence et les facteurs associés aux infections chez les patients transplantés d'organes solides (3). L'ensemble des patients ayant reçu une transplantation entre 2003 et 2005 ont été inclus. Sur la période d'étude, 2169 transplantés d'organes (2702 au total) parmi lesquels 1092 transplantés de rein, ont été suivis plus de 6 mois. L'incidence des infections, toutes causes confondues, chez les transplantés de rein était de 4.91 infections/ 1000 jours de transplantation pendant la période précoce (premier mois), 2.02 infections/1000 jours de transplantation sur la période

intermédiaire (2 à 6 mois post transplantation) et de 0.28 infections/ 1000 jours de transplantation sur la période tardive (>6 mois post transplantation). Ces taux d'incidence étaient systématiquement inférieurs à la moyenne des taux d'incidence de l'ensemble des transplantés d'organe solide. Les facteurs associés au développement d'une infection dans la période tardive chez les patients transplantés de rein et ou de pancréas étaient un mismatch CMV donneur receveur, un traitement immunosuppresseur comprenant du sirolimus, au moins deux épisodes d'infections bactériennes durant la période précoce et enfin une dysfonction chronique du greffon.

Plus récemment, une étude réalisée à partir des données de la cohorte nationale suisse a décrit les infections et leur délai de survenue au cours de la première année au décours d'une transplantation d'organe solide (4). Parmi les 3541 patients suivis, 1612 avaient reçu une transplantation rénale, et ont présenté à un an de suivi un total de 1964 infections . Le taux d'incidence des infections était maximum le premier mois post transplantation avec 8.3 (7.5-9.2) infections/1000 jours, puis décroissant jusqu'à 2.1 (1.9-2.4) infections/1000 jours post transplantation sur la période 6-12 mois. Chez les transplantés rénaux, les infections urinaires représentaient environ 70% des infections bactériennes, suivies des bactériémies, des infections intra-abdominales et des infections respiratoires. La prévalence des infections à BLSE parmi les infections documentées à entérobactéries était de 15% environ. Le second groupe de pathogènes le plus fréquent était les infections virales dont la répartition des sites d'infection chez l'ensemble des transplantés était par ordre décroissant : les infections cutanéomuqueuses (23%), les infections respiratoires (22%), les infections hépatiques (22%). Les virus du groupe herpès étaient les plus fréquents avec 51% de infections possibles ou prouvées, et le CMV représentait le principal pathogène. Parmi les transplantés de rein, 16% ont présenté une virémie à BK virus et 6% ont présenté

une néphrite à BK virus prouvée. Les infections fongiques représentaient 7.5% des infections dans l'ensemble de la population d'étude.

Une étude récente utilisant les données nationales de l'assurance maladie américaine a étudié les facteurs associés à la survenue d'infections chez 141661 transplantés rénaux américains entre 1999 et 2014 (5). Parmi ceux-ci, 96 440 ont présenté au moins une infection au décours de leur transplantation, avec une incidence cumulée à 3 mois de 36.9%, de 53.7% à un an et de 78% à 5 ans. Les infections les plus fréquentes étaient par ordre décroissant : les infections urinaires (46.8%), les infections respiratoires (28.2%), les sepsis (25.6%), les infections digestives (13.7%), et les infections par le CMV (10.7%). Les facteurs associés à la survenue d'une infection après ajustement étaient l'âge (OR= 1.14 (1.13-1.16)), et le sexe féminin (OR=1.75 (1.69-1.82)). Parmi les maladies rénales sous-jacentes, les groupes plus à risque de développer des infections étaient la néphropathie diabétique (OR=1.42 (1.35-1.49)), et la néphropathie hypertensive (OR=1.08 (1.03-1.14)), alors que la polykystose rénale était associée à une moindre survenue d'infections (OR=0.88 (0.83-0.93)). Les autres facteurs associés à un surrisque d'infection étaient un antécédent d'hépatite B (OR=2.34 (1.85-2.96)), un antécédent d'hépatite C (OR=2.54 (2.29-2.82)), la durée de dialyse pré transplantation (OR/année=1.03 (1.02-1.04)), le niveau d'allo-immunisation HLA (pourcentage du PRA, panel reactive antibody) (OR/10%=1.01 (1.00-1.01)). Parmi les caractéristiques des donneurs, l'âge (OR/10years=1.05 (1.04-1.07)) et le sexe féminin (OR=1.06(1.03-1.08)) étaient également associés, alors qu'un donneur vivant était associé à un moindre risque d'infection (OR=0.73 (0.67 ; 0.79)).

3. Histoire naturelle des infections chez le transplanté rénal

Chez le patient transplanté rénal, le risque d'infection évolue au cours du temps : Il existe une phase initiale précoce marquée par les infections nosocomiales et les complications post-opératoires, puis l'année qui suit la transplantation est la période la plus à risque d'infections, opportunistes ou non, et ce risque diminue progressivement les années suivantes (4–6). Il n'existe malheureusement pas d'outils performant pour mesurer le risque infectieux à un moment donné et cette évaluation repose principalement sur l'évaluation par le clinicien. L'évolution du risque infectieux dépend principalement de l'âge, du sexe, des comorbidités et antécédents du receveur, des traitements immunosuppresseurs, des expositions environnementales et des prophylaxies reçues.

Les infections issues du donneur

Elles correspondent la plupart du temps à des infections latentes/quiescentes chez le donneur et peuvent se réactiver du fait de l'immunosuppression et/ou aussi du mismatch immunitaire. Parmi elles prédominent notamment les virus latents, en premier lieu desquels le *cytomégalo*virus (CMV) (7), EBV et HHV8, mais également des bactéries comme la tuberculose ou des champignons (histoplasmosse, coccidioidomycose). Il peut aussi s'agir d'infections actives méconnues chez le donneur au moment du prélèvement (west nile virus, rage) (8). Enfin certains parasites comme *trypanosoma cruzi* ou *strongyloides stercoralis* peuvent aussi être transmis par le greffon (9,10).

Les infections nosocomiales et associées à la chirurgie

Elles surviennent principalement dans le mois qui suit la transplantation rénale. Les bactéries responsables de ces infections sont plus souvent résistantes puisque acquises en milieu hospitalier. Le phénotype de résistance de ces pathogènes dépend notamment de la colonisation du patient mais aussi de l'épidémiologie microbienne de l'établissement pratiquant la transplantation (11). Les infections à *Clostridium difficile* sont également plus fréquentes durant cette période (12).

Les infections à *Candida* du liquide de conservation du greffon sont d'une particulière gravité, car elles peuvent être responsables d'anévrysmes mycotiques de la zone anastomotique dont le pronostic est parfois sombre (13). De ce fait, la culture mycologique du liquide de conservation est désormais systématique.

Les infections communautaires

Il s'agit d'infections qui peuvent être acquises chez des personnes non immunodéprimées, comme les pathogènes respiratoires responsables d'épidémies saisonnières, mais dont l'incidence et la sévérité peuvent être augmentés après transplantation rénale, comme les pyélonéphrites et les pneumopathies (4,5,14).

Les infections opportunistes

Il s'agit d'infections peu fréquentes ou inexistantes chez les patients immunocompétents, mais pour lesquelles la présentation est fortement modifiée et plus sévère du fait de l'immunosuppression. Il peut s'agir de réactivation de pathogènes issus du receveur ou du donneur. Les réactivations *CMV* sont les plus fréquentes, raison pour laquelle une prévention est instaurée les premiers mois après la transplantation (15). La néphrite à *BK* virus est également un souci majeur, dont l'incidence est diminuée par une surveillance virale étroite avec adaptation de

l'immunosuppression en cas de réplication virale (16,17). Il peut également s'agir de lymphoproliférations post-transplantations induites par l'*EBV* (18,19), ou les sarcomes de Kaposi induits par *HHV8*. La réactivation de *Mycobacterium tuberculosis* est également classique, bien que plus rare, aussi il est ainsi recommandé de traiter une tuberculose latente avant transplantation. Il existe également un risque de réactivation de protozoaires tissulaires comme *Toxoplasma gondii*, ou d'infections fongiques comme certaines mycoses endémiques (*Histoplasma capsulatum*, *Coccidioides immitis*, et *Paracoccidioides brasiliensis*) (20).

D'autres infections vont présenter une symptomatologie modifiée, par exemple une hépatite chronique par le virus de l'hépatite E, habituellement responsable d'infection aiguë(21), ou une diarrhée chronique et non une simple gastro entérite aiguë liée au norovirus (22,23). Ces infections peuvent être acquises dans l'environnement par exposition à des pathogènes environnementaux ou respiratoires opportunistes fongiques comme *Aspergillus*, *pneumocystosis* ou *Cryptococcus* (24–26).

Chronologie de la survenue des infections

La chronologie des infections a évolué ces dernières années, du fait des préventions, de la modification des immunosuppresseurs, et des profils des patients. Classiquement, le premier mois suivant la transplantation, la majorité du risque infectieux est porté par les infections de la zone opératoire, les pyélonéphrites et pneumopathies, les infections issues du donneur, les infections à *Candida* et la colite à *Clostridioides difficile*.

Durant les 12 mois suivants, qui correspondent à la période de plus forte immunosuppression, les pyélonéphrites et pneumopathies restent les infections les plus fréquentes. Les infections virales : *CMV*, néphrites à *polyomavirus BK*, *HSV*, sont

une préoccupation majeure, bien que les prophylaxies aient une efficacité certaine. Le risque d'infection par *pneumocystis* est à ce jour faible compte tenu d'une prophylaxie systématique par cotrimoxazole durant cette période. Cette prophylaxie a également probablement un impact sur l'incidence des infections urinaires, bien que les souches résistantes soient non rares, avec environ 20% de résistance à E. coli pour le bactrim dans les souches isolées de prélèvements cliniques (27). Cette période est celle durant laquelle le risque d'infection fongique par *aspergillus* et *candida* est la plus importante (20,24). Le risque d'infection fongique reste néanmoins faible avec une incidence cumulée à un an de 1% chez le transplanté rénale, contre 3.1% en moyenne chez l'ensemble des transplantés d'organe solide (20), et ne justifie pas à l'heure actuelle de prophylaxie spécifique après transplantation rénale, à la différence des transplantations hépatiques et pulmonaires (28–30).

Au-delà de la première année, le risque infectieux diminue progressivement en parallèle d'une certaine restauration immunitaire. Il persiste tout de même un risque infectieux augmenté en comparaison de la population générale. Ce risque est variable d'un patient à l'autre et dépendra notamment du niveau d'immunosuppression, lié au traitement reçu, à l'âge et aux comorbidités des patients.

I. INTRODUCTION

Kidney transplant recipients are at increased risk of infections due to immunosuppressive regimen, comorbidities, and derived donor infections (6). Infectious diseases may represent the second cause of mortality after cardio-vascular diseases and before neoplasia (2), and are reported to be associated with a risk of graft dysfunction and loss (31,32). As previously described, two recently published swiss and american cohorts confirmed that urinary tract infection is from far the most common cause of post-transplant infectious complications (33), with an incidence of transplant pyelonephritis of 3.7 per patient/year (34), followed by pneumonia, and skin and soft tissues infection (4,5,14). Opportunistic infections are also a frequent burden after kidney transplantation. They are caused by unusual pathogens, or by common pathogens but with unusual or more severe presentations (21,22,35). Opportunistic infections prevalence varies between 5.5% and 12.2% of KTR in the different published series, depending on the period of follow-up and the nosology of pathogens included (36–38). Indeed, the spectrum of OI has changed over the years, with the use of prophylaxis against CMV and pneumocystis pneumonia (15,39) as well as specific BKV monitoring (17).

Opportunistic infections may be particularly severe with a bad prognosis. While association of BK virus nephritis and graft loss is now evident (40), other studies suggest that CMV disease (30-32) as well as other opportunistic infections (34) might be associated with graft loss, but data are conflicting on this point (35). In general OI series, there is no evidence for an overall increased risk of mortality (36,37). However, a poor survival has been described with specific OI, including fungal infections (25,41–43).

Specific risk factors for the most prevalent OI vary, depending on the pathogen: serological mismatch concerning CMV disease (44,45), transport fluid contamination for invasive candidiasis (13,46), steroids, neutropenia and acute rejection episodes for invasive aspergillosis, and an history of rejection or a CMV disease for pneumocystis pneumonia (47). In a french monocentric cohort of KTR, the only factor associated with the occurrence of any opportunistic infection was extended donor criteria (ECD), whereas high blood lymphocyte count at the time of transplantation was associated with less OI. Age, recipients medical history and immunosuppressive regimen were not associated with the risk of OI, after adjusting on confounding factors (37).

Among patients presenting an opportunistic infection, 7 to 11% will present at least another OI according to published data (37,38), but very few data exist regarding their descriptions and factors associated with a second OI. Some data suggest an association between CMV disease and the risk for fungal infection in liver transplant recipients (48), and CMV infection might be associated with pneumocystis pneumonia (47).

Thus, the aim of our study is to describe epidemiology of patients with opportunistic infections, especially with more than one OI, and to determinate the factors associated with multiple OI in KTR.

II. MATERIAL AND METHODS

1. Inclusion and exclusion criteria

All patients receiving a kidney transplantation between February 1997 and December 2015 in one of the 6 participating centers, accepting follow-up in DIVAT cohort and with available informations regarding the occurrence of infections, were eligible for inclusion in this study.

Period of inclusion were different for the different centers as detailed below:

- Lyon: august 2006-october 2015
- Montpellier: january 1998-october 2015
- Nancy: march 2000-october 2015
- Nantes: january 1997-december 2015
- Necker: february 1997-december 2015
- Toulouse: february 1997- november 2011

Follow up ended on January 30th 2018.

Patients younger than 18 years old and/or receiving multi-organ transplantation were not included in the study.

2. DIVAT cohort

DIVAT (Données Informatisées et VALides en Transplantation) is a french data base, used for follow-up of kidney or pancreas transplantation recipients. This cohort was started in the end of the 90's. It gathered patients from nine French teaching hospital Lyon, Grenoble, Montpellier, Nancy, Nantes, Nice, Necker Hospital, Saint-Louis

hospital and Toulouse. Its main objective is to allow epidemiological research in the field of transplantation, focusing on clinical outcome (graft rejection, graft survival, patients survival), therapeutic strategies and public health problems. Concerning all patients included, donor's clinical and epidemiological characteristics were recorded. Concerning graft recipients, medical history, clinical characteristics, and immunosuppressive regimen at the day of transplantation and during the follow-up were recorded, as detailed in the next section. Data were systematically collected every three months during the first year of follow-up and then once a year until last follow-up. Clinical complications, including detailed infectious complications, as well as graft rejection episodes and their treatments, were recorded in the database at the date of the reported complication.

3. Data collection

I. General data collected

For all included patients, following variables were collected:

- Donor variables: gender, age, type of donor (deceased or living donor), extended or standard donor criteria*, and serological status for HIV, HBV, HCV, CMV and EBV.
- Recipient variables: gender, date of birth, underlying renal disease, medical history (cardio vascular, metabolic, neoplasia), serological status for HIV, HBV, HCV, CMV and EBV, duration and type of EER before transplantation, body mass index (BMI).
- Transplantation variables: graft rank, cold ischemia, sudden or delayed graft function, induction treatment.

- Follow-up data: creatininemia ($\mu\text{mol/L}$), Body mass index (BMI), immunosuppressive regimen, acute or chronic rejection episode and associated treatment, any medical or surgical complication, according to predefined thesaurus.

Details of predefined thesaurus are available in annexe 1

* Expanded criteria donor (ECD) was defined as donors older than 60 years, or between 50 and 60 years, and two of the three following criteria: (i) hypertension; (ii) pre-retrieval serum creatinine $> 1.50 \text{ mg/dL}$; and (iii) cerebrovascular cause of brain death (49).

II. Systematic infectious diseases collection

A specific thesaurus was created to allow a uniform and systematic collection of infectious diseases complications. Input mask of the electronic form was composed of the following items , as detailed in **annexe 2** :

- Infected organ
- Type of pathogen: bacteria, virus, fungi, parasite, undetermined.
- Pathogen identification

Following situations were not included in the data collection:

- Asymptomatic viremia. Thus BK and CMV viremia without disease were not recorded.
- Bacterial colonization
- Upper respiratory tract infections and lower urinary tract infections
- HSV uncomplicated infections, including labial and genital infections.

To evaluate the quality of data completion, we performed a cross validation in each center using biological and medical files to ascertain the validity of the reported

infections. For pathogens such as CMV, and BKV, medical files and histological reports were verified to differentiate viremia and diseases.

In case of recurrence of the same pathogen, and when clinical information was not available to differentiate a prolonged infection from a novel clinical event, we systematically eliminated from the analysis the reported infection as follow:

- In case of recurrence within one month for *Clostridioides difficile*.
- In case of recurrence within two months for VZV
- In case of recurrence within 6 months for: *Aspergillus*, *CMV*, *HHV8*.

III. Opportunistic infections definition

Opportunistic infections were for each group of pathogens:

VIRAL INFECTIONS :

- *BK virus* nephropathy: Banff study group diagnosis criteria (16).
- *CMV* disease: international transplantation society consensus guidelines (15)
- VZV: PCR or clinical diagnosis.
- *HSV* invasive infection (meningitis; oesophagitis; hepatitis): clinical symptoms and positive PCR
- *Kaposi* sarcoma: histology (immunostaining/ molecular biology, ...) (50)
- *Norovirus*: PCR on stools or digestive biopsy and symptoms as diarrhea or marked weight loss.
- *HEV* (hepatite E): hepatitis and positive PCR in blood and/or stool.
- *JCV* nephropathy: positive PCR in kidney biopsy

BACTERIAL INFECTIONS:

-*Mycobacterial/ Nocardia* infection: clinical or radiological signs and bacteriological culture or molecular biology

-*Listeria monocytogenes*: clinical or radiological signs and bacteriological culture or molecular biology

-*Clostridioides difficile* infections: diarrhea and a microbiological diagnosis including a toxin based test (51)

FUNGAL INFECTIONS:

- Invasive fungal disease including candida, endemic mycosis, aspergillosis, cryptococcosis, other mold infections: EORTC diagnosis criteria (52). Concerning *Candida* infection, muco cutaneous candida infections (oral, oesophageal) or urinary tract infections were not considered as invasive fungal infections and were not included in the analysis.

- Pneumocystosis: ECIL diagnosis criteria(53).

- Intestinal Microsporidiosis: diarrhoea and stool positive microsporidiosis PCR or direct stool examination

PARASITIC INFECTIONS:

- Cryptosporidiosis: diarrhea and direct stool examination or PCR

- Toxoplasmosis: clinical or radiological signs and proven infection (parasitologic diagnosis or PCR) or probable.

There was no information available regarding OI prophylaxis procedure because of the absence of national standardisation and of changing patterns in each of the centers during the study period.

IV. Multiple OI definition

Patients were considered to present a multiple OI if they presented at list two OI. This second or more OI was called recurrence of OI. If the two first OI occurred at the same date, patients were included in the multiple OI group, but were not included in the analysis because they could not be analysed using a time varying COX model.

4. Statistical analysis

Study population was described using median and interquartile range [IQR] or mean and standard deviation (SD) for quantitative variable, and frequencies and percentages for categorical variables. Factors associated with the new occurrence of an opportunistic infection were analysed using a univariate Cox proportional model. Study entry time was the date of the first reported opportunistic infection as defined above. End of follow-up occurred when patients died; in case of loss of graft function defined as return to dialysis or data were right censored at the date of end of follow-up in the registry. Study endpoint was defined as the date of occurrence of a new opportunistic infection. Time varying Cox proportional model was built to evaluate factors associated in time-to-event analysis with the primary end point. Proportionality rule was tested for all variables intended to be used in the model using Schoenfeld's residuals testing. Considering continuous variables, a nonlinear association was evaluated using a

graphical evaluation. Factors associated with the outcome in univariate analysis with a p-value equal or less than 0.20 were included in the multivariate analysis. A stepwise backward procedure was applied for the final model data selection. Multivariate analysis was stratified by centre to take into account differences and results were given as hazard ratios (HR) associated with 95% confidence interval (95% CI). Statistical analysis were performed using Stata15 and graphical representation were performed using R (version 4.0.2, R foundation for Statistical Computing).

5. Ethic

The CNIL (commission nationale informatique et liberté) gave a favourable opinion (09-17-2004, number 891735, DIVAT network: 10.16.618) for data collection in DIVAT cohort. Patients consent regarding the access to medical records, data collection and biocollection was obtained. Medical record anonymisation was performed while data were collected

III. RESULTS

1. Population selection and description

Among the 9752 patients included in DIVAT cohort during the follow-up period, 211 were not eligible to inclusion because of missing data regarding the infectious status. Among the 9541 left, 1872 (19.6%) patients presented at least one opportunistic infection as previously defined. Among them, 58 did not have follow-up consultation after their first opportunistic infection, thus their inclusion in the survival analysis was not possible. Flowchart is described in figure 1.

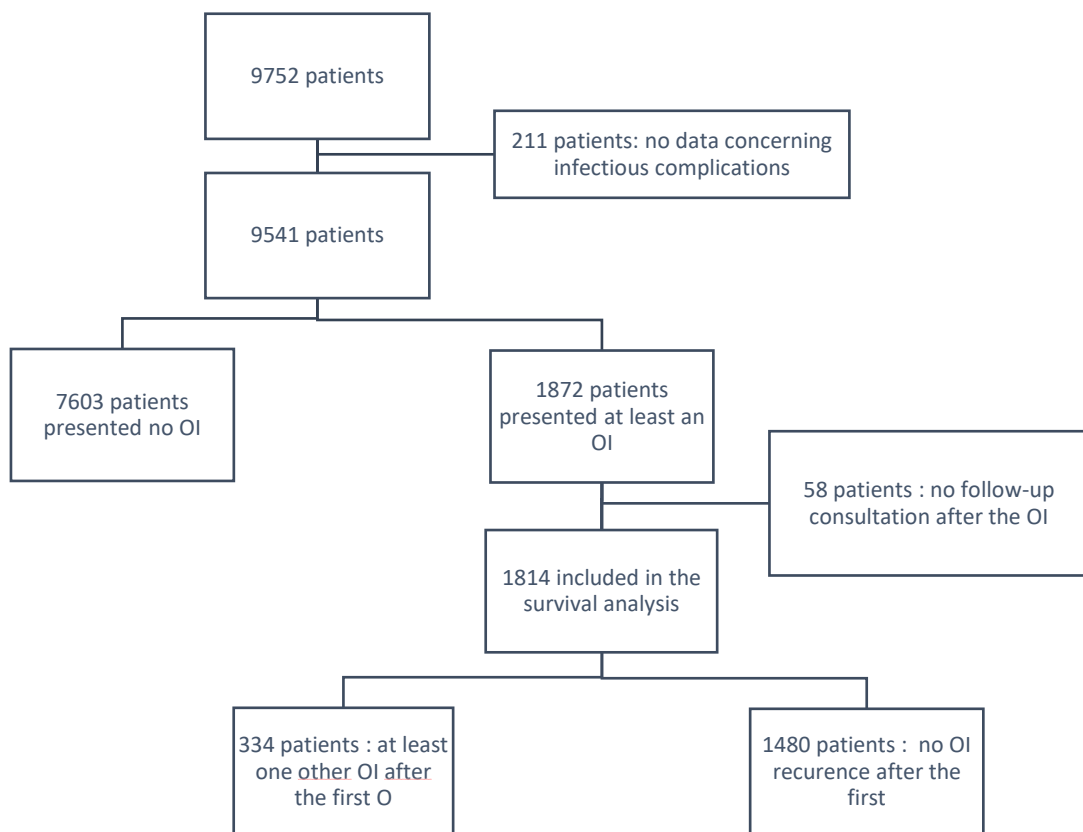


Figure 1: Flowchart

Patients and transplantation characteristics

Among the 1872 patients with at least one OI, mean age at transplantation was 51.8 years \pm 13.9, 1152 (61.5%) were men, and 858 (46.0%) patients had a BMI between 20 and 25 kg/m² at transplantation. Most frequent underlying kidney disease were glomerular nephropathy for 559 patients (29.9%) followed by polycystic kidney disease for 305 (16.3%), and interstitial nephropathy for 222 (11.9%), while 1493 (83.2 %) had an history of high blood pressure (HBP) and 259 (14.4%) an history of diabetes the day of transplantation. Most patients (n=1596, 85.3%) received a kidney transplantation for the first time and 243 (12.6%) received a living donor kidney. Induction treatment consisted in a non-depleting agent for 904 (48.3%) patients, in a depleting agent for 802 (42.9%) and none for 165 (8.8%).

Follow up data

Three months after transplantation, mean creatininemia was 145.8 μ mol/l \pm 56.7. Rejections (either humoral or cellular) requiring a treatment were observed in 410 (21.9%) patients before the first opportunistic infection.

Three months after transplantation, maintenance immunosuppressive regimen was based on calcineurin inhibitors in most of the cases, with 1148 (62.1%) patients receiving tacrolimus and 603 (32.6%) receiving ciclosporine, 115 patients (6.2%) receiving an mTOR inhibitor, 29 (1.6%) belatacept, and 4 (0.2%) JAK3 inhibitor. Most of the patients were also receiving antimetabolite agents, with 1644 (90.2%) receiving mycophenolate mofetil and 59 (3.2%) azathioprine. Most of patients were under steroid therapy (n=1628, 87.9%).

Median follow-up time after the first OI was 3.3years and the cumulative person/year was 7690.9. Details of demographic and clinical characteristics are reported in **table1**.

Table 1 Demographic and medical characteristics of the population

| | total | Number of patients |
|---|-------------|--------------------|
| Number of patients, N(%) | 1872 | 1872 |
| Age (year), meanSD | 51.8±13.9 | 1872 |
| Male gender, N(%) | 1152 (61.5) | 1872 |
| BMI, N(%) | | 1865 |
| <17 | 36 (1.9) | |
| 18-20 | 269 (14.4) | |
| 21-25 | 858 (46.0) | |
| 26-30 | 504 (27.0) | |
| >30 | 198 (10.6) | |
| Initial nephropathy, N(%) | | 1872 |
| Glomerular nephropathy | 559 (29.9) | |
| Interstitial nephropathy | 222 (11.9) | |
| Polycystic kidney disease | 305 (16.3) | |
| Vascular nephropathy | 146 (7.8) | |
| Diabetic nephropathy | 148 (7.9) | |
| Others | 191 (10.2) | |
| Unknown | 301 (16.1) | |
| Diabetes history, N (%) | 259 (14.4) | 1795 |
| High blood pressure history, N (%) | 1493 (83.2) | 1795 |
| Transplantation rank, N(%) | | 1872 |
| 1 | 1596 (85.3) | |
| ≥2 | 276 (14.7) | |
| Donor age, mean (SD) | 53.4±16.0 | 1864 |
| Living donor | 243 (12.6) | 1868 |
| Cold ischemia delay, mean (SD) | 18.5± 9.3 | 1854 |
| Induction treatment, N(%) | | 1871 |
| None | 165 (8.8) | |
| Depleting induction | 904 (48.3) | |
| Non depleting induction | 802 (42.9) | |
| Maintenance therapy at M3 | | 1850 |
| Calcineurin inhibitor | 1751 (94.7) | |
| Ciclosporin | 603 (32.6) | |
| Tacrolimus | 1148 (62.1) | |
| mTOR inhibitor | 112 (6.2) | |

| | | |
|---|-------------|------|
| Belatacept | 29 (1.6) | |
| JAK3 | 4 (0.2) | |
| Antimetabolite agents | | |
| Mycophenolate mofetil | 1644 (90.2) | 1822 |
| Azathioprine | 59 (3.2) | 1855 |
| Steroids | 1628 (87.9) | 1852 |
| Creatininemia at M3, $\mu\text{mol/L}$ | 145.8+-56.7 | 1811 |
| Creatininemia at M6, $\mu\text{mol/L}$ | 146.0+-56.3 | 1791 |
| Creatininemia at M12, $\mu\text{mol/L}$ | 149.0+-60.6 | 1772 |
| Graft rejection, N(%) | 559 (29.9) | 1872 |
| Before first OI | 410 (21.9) | |
| After first OI | 118 (6.3) | |
| Rejection, missing date | 32 (1.7) | |
| <hr/> | | |
| Follow-up (year), median | 3.33 | |
| Patient-year, N | 7690.9 | |
| <hr/> | | |

Among the 1872 patients presenting at least one opportunistic infection, most of them were followed at Necker hospital, Paris (n=629, 33.6%), followed by Nantes (n=372, 20%), Montpellier (n=280, 15%), Nancy and Toulouse (n=209, 11.2% each) and Lyon (n=173, 9.2%). Details of centre's total number of patients and of patients with IO, as well as period of inclusion is reported in **table 2**.

Table 2 : Centers data

| Center | Effective (DIVAT cohort) | Number of OI |
|--------------------|---------------------------------|---------------------|
| Necker | 2245 (23.5) | 629 (33,6) |
| Nantes | 2167 (22.7) | 372 (20,0) |
| Montpellier | 1662 (17.4) | 280 (15,0) |
| Toulouse | 1231 (12.9) | 209 (11,2) |
| Nancy | 1220 (12.8) | 209 (11,2) |
| Lyon | 1015 (10.6) | 173 (9.2) |

2. Description of opportunistic infections

During follow up, 1872 patients presented at least one opportunistic infection, and 334 of them presented more than one opportunistic infection, leading to 2292 opportunistic infections in total. The maximum number of cumulated opportunistic infections was 5, and the incidence rate of recurrence was 4.2 (3.2-4.7) per 100 patient year. Number of OI are described in **table 3**.

Table 3: cumul of OI per patient

| Number of OI | Number of patients (%) |
|---------------------|-------------------------------|
| 1 OI | 1538 (82.2) |
| 2 OI | 270 (14.4) |
| 3 OI | 47 (2.5) |
| 4 OI | 12 (0.6) |
| 5 OI | 5 (0.3) |

Description of first opportunistic infection

First OI occurred in a median delay of 382 days [131; 1242] after transplantation. Interestingly, this first OI occurred earlier in patients with multiple OI (356 [129; 1111]) as compared to patients with a single OI (405.5 [131 ; 1277]).

Concerning the diagnosis of opportunistic infections, 22 different pathogens were documented. In the whole population, for the 1st OI, viral infections were the most frequent (n=1395, 73.7%) followed by fungal (n=254, 13.4%) bacterial (n=217, 11.5%) and parasitic (n=26, 1.4%) infections. The most prevalent pathogen was *CMV* (n=512), followed by *VZV* (n=466), *BK virus* nephropathy (n=181), *Clostridioides difficile* (n=138), *Norovirus* (n=127), and *Pneumocystis* (n=100). Details of first opportunistic infections and delay of diagnosis are reported in Figure 2.

| Pathogen | Number of patients (%) | Median delay after transplantation, days [IQR] |
|--|------------------------|--|
| Viral infections | | |
| CMV | 512 (27.0) | 162 [60 ; 314.5] |
| BKV | 181 (9.6) | 267 [130 ; 507] |
| Kaposi | 30 (1.6) | 409 [234 ; 855] |
| HSV | 15 (0.8) | 699 [428 ; 3453] |
| VZV | 466 (24.6) | 705 [296 ; 1483] |
| Norovirus | 127 (6.7) | 1120.5 [318 ; 2221] |
| JCV | 2 (0.1) | 1190 [1145 ; 1235] |
| VHE | 62 (3.3) | 1629 [751 ; 2618] |
| Fungal and parasitic infections | | |
| Aspergillus | 77 (4.1) | 365 [136 ; 1435] |
| Other molds | 7 (0.4) | 508.5 [209.5 ; 1641] |
| Toxoplasma | 15 (0.8) | 537 [209 ; 1757] |
| Cryptococcus | 14 (0.7) | 637.5 [248 ; 1122] |
| Pneumocystis | 100 (5.3) | 730 [273.5 ; 2155] |
| Microsporidium | 34 (1.8) | 955 [425 ; 1441] |
| Candida | 13 (0.6) | 1099 [129 ; 2296] |
| Cryptosporidium | 20 (1.1) | 1231.5 [376 ; 1717] |
| Bacterial infections | | |
| Clostridioides difficile | 138 (7.3) | 216 [33 ; 1330] |
| Nocardia | 14 (0.7) | 395 [201 ; 1897] |
| Listeria | 2 (0.1) | 502.5 [292 ; 713] |
| Tuberculous mycobacteria | 47 (2.5) | 584 [213 ; 1275] |
| Non tuberculous mycobacteria | 16 (0.9) | 824 [182 ; 2362] |

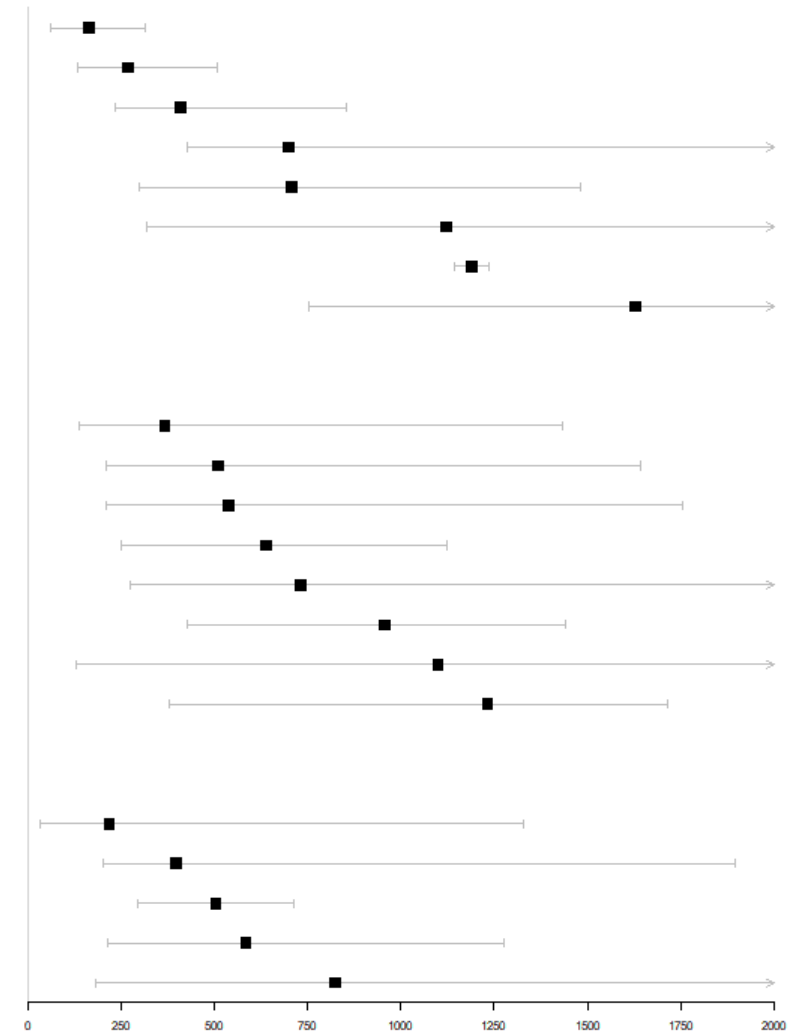


Figure 2 Description and time of occurrence of the first OI in the general population

In patients with single OI, main first OI were *CMV* (n=419, 27.2%), *VZV* (n=410, 26.7%), *BKV* (n=154, 10.0%), *norovirus* (n=95, 6.2%), *Clostridioides difficile* (n=91, 5.9%), and *pneumocystis* (n=79, 5.1%). In patients with multiple OI, main first OI were *CMV* (n=93, 26.2%), *VZV* (n=56, 15.8%), *Clostridioides difficile* (n=47, 13.3%), *norovirus* (n=32, 9.0%), and *BKV* (n=27, 7.6%). For some pathogens, there was notable differences in the delay from transplantation between the two groups. In case of multiple OI, VHE hepatitis occurred earlier (309 days [119 ; 1611] vs 1737 days [1000 ; 3026,5]), as for pneumocystis pneumonia (472 days [274 ; 1474] vs 797 days [273 ; 2339]), and as for *Clostridioides difficile* colitis (103 days [19 ; 519] vs 357 [65 ; 1517]). Differences concerning type and delay of first OI between multiple and single OI group are described in Figure 3 for virus, Figure 4 for fungus and parasites and Figure 5 for bacteria.

| Viral infections | Number of patients (%) | Median delay after transplantation, days [IQR] |
|------------------|------------------------|--|
| CMV | | |
| single OI | 419 (27,2) | 153 [58 ; 296] |
| multiple OI | 93 (26.2) | 221 [85 ; 530] |
| BKV | | |
| single OI | 154 (10.0) | 246,5 [128 ; 491] |
| multiple OI | 27 (7.6) | 320 [160 ; 556] |
| Kaposi | | |
| single OI | 19 (1,2) | 433 [249 ; 855] |
| multiple OI | 11 (3,1) | 309 [119 ; 1611] |
| HSV | | |
| single OI | 10 (0,6) | 572,5 [428 ; 3903] |
| multiple OI | 5 (1,4) | 1256 [699 ; 1276] |
| VZV | | |
| single OI | 410 (26,7) | 712 [303 ; 1546] |
| multiple OI | 56 (15.8) | 640 [248 ; 1015] |
| JCV | | |
| single OI | 2 (0,1) | 1190 [1145 ; 1235] |
| multiple OI | | / |
| Norovirus | | |
| single OI | 95 (6,2) | 1229 [456 ; 2220] |
| multiple OI | 32 (9.0) | 975.5 [273.5 ; 2228] |
| VHE | | |
| single OI | 56 (3,6) | 1737 [1000 ; 3026,5] |
| multiple OI | 6 (1,7) | 317,5 [161 ; 721] |

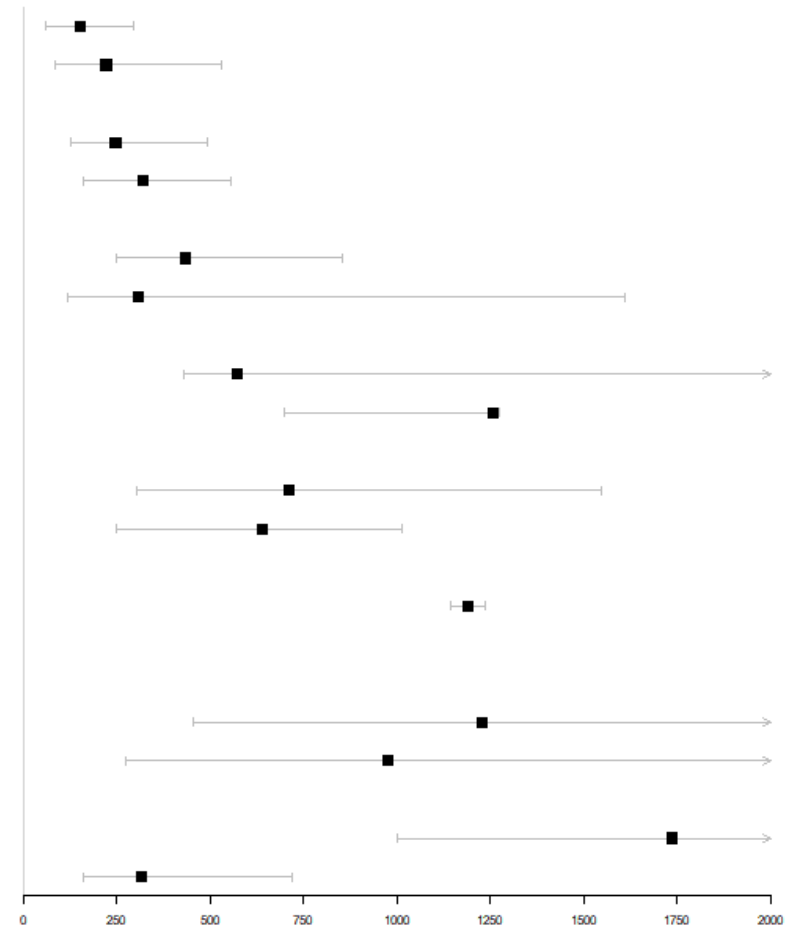


Figure 3 : Description and delay of the first OI in single or multiple OI patients, viral infections

| Pathogen | Number of patients (%) | Median delay after transplantation, days [IQR] |
|-----------------|------------------------|--|
| Aspergillus | | |
| single OI | 60 (3.9) | 338.5 [132 ; 1303.5] |
| multiple OI | 17 (4.8) | 369 [139 ; 1702] |
| Other molds | | |
| single OI | 14 (1.1) | 565.5 [210 ; 1757] |
| multiple OI | 2 (0.6) | 206,5 [6 ; 407] |
| Toxoplasmosis | | |
| single OI | 5 (0.3) | 718 [288 ; 1763] |
| multiple OI | 1 (0.3) | 27 |
| Pneumocystis | | |
| single OI | 79 (5.1) | 797 [273 ; 2339] |
| multiple OI | 21 (5.9) | 472 [274 ; 1474] |
| Cryptococcus | | |
| single OI | 12 (0.8) | 830 [345,5 ; 1544] |
| multiple OI | 2 (0.6) | 253 [137 ; 369] |
| Microsporidium | | |
| single OI | 25 (1.6) | 945 [425 ; 1441] |
| multiple OI | 9 (2.5) | 1094 [696 ; 1429] |
| Candida | | |
| single OI | 9 (0.6) | 1099 [327 ; 5161] |
| multiple OI | 4 (1.1) | 623 [65,5 ; 1706.5] |
| Cryptosporidium | | |
| single OI | 17 (1.1) | 1235 [427 ; 1726] |
| multiple OI | 3 (0.9) | 238 [43 ; 1432] |

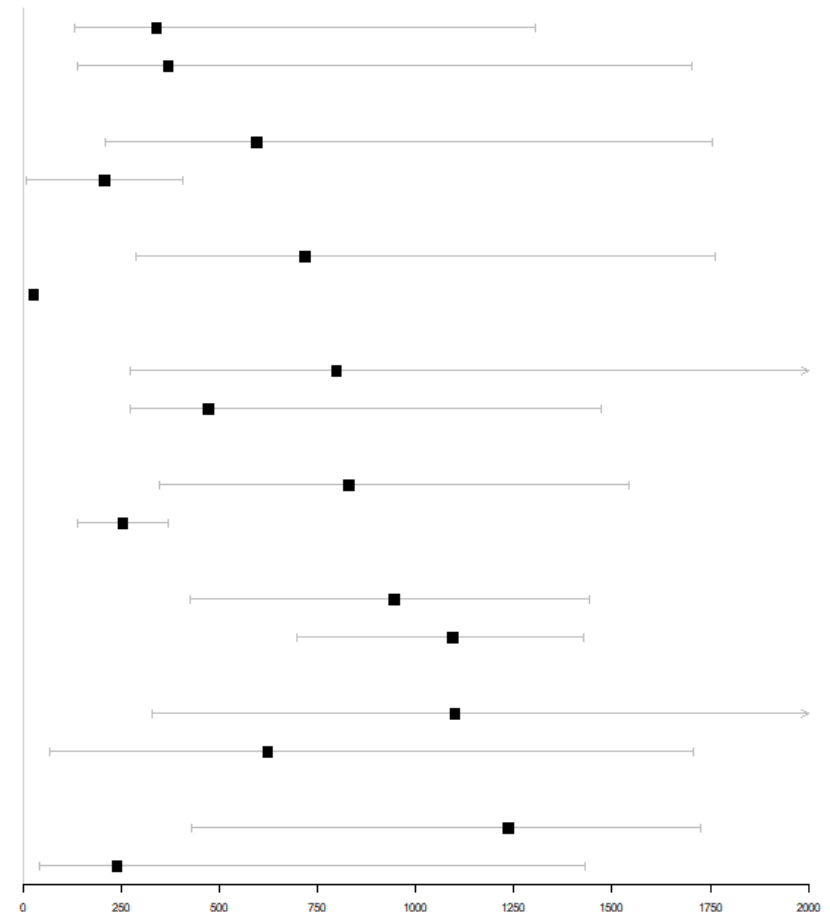


Figure 4: Description and delay of the first OI in single or multiple OI patients, fungal and parasitic infections

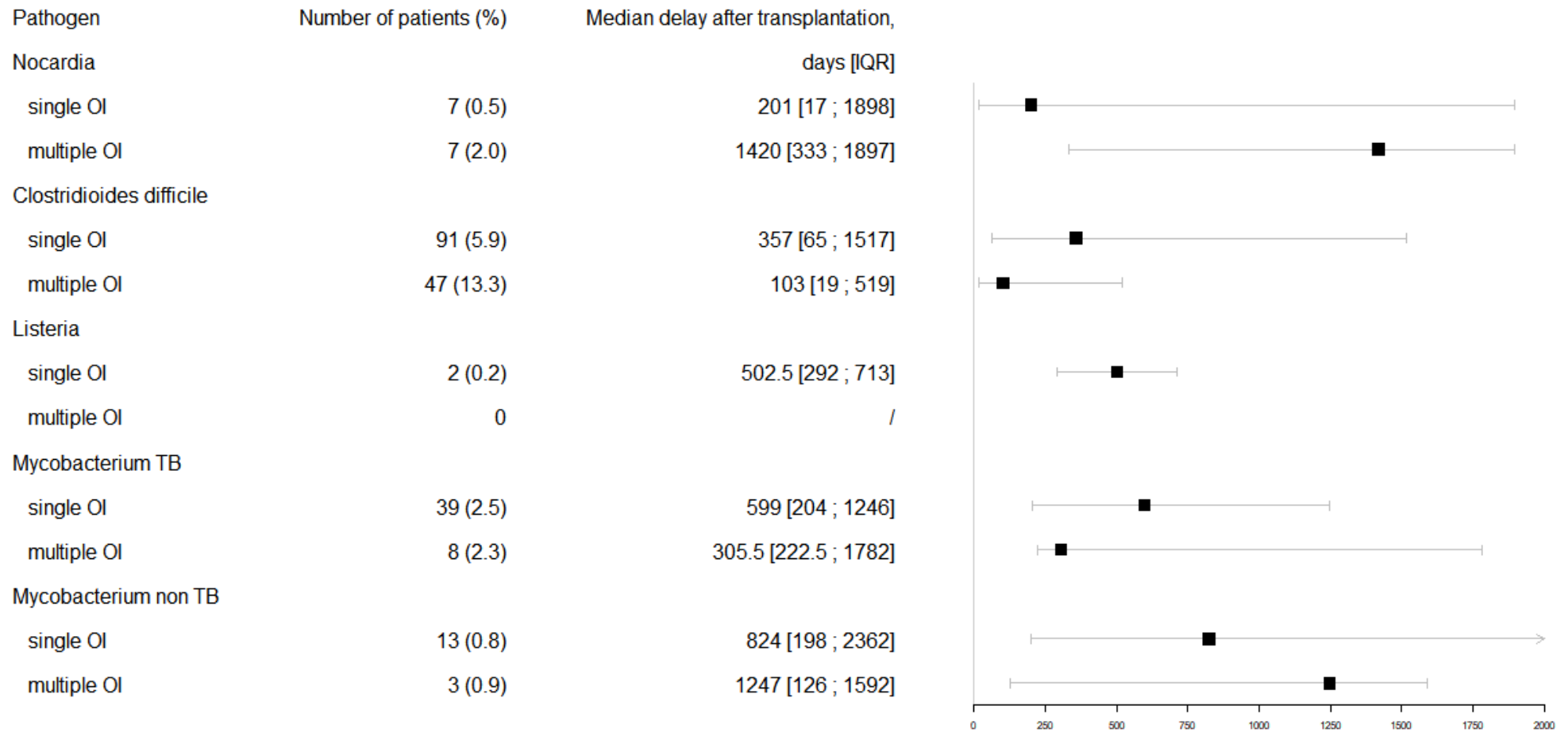


Figure 5: Description and delay of the first OI in single or multiple OI patients, fungal and parasitic infections

In all, 334 patients had at least two OI, called “recurrent OI”. After the first OI, following OI were viral (n=243, 60.7%), fungal (n=78, 19.5%), bacterial (n=76, 19.0%), and parasitic (n=3, 0.8%). Median delay from transplantation to any of the second or more OI was 1492 days [597; 2376], and median delay from the first OI to any of the second or more OI was 601 days [184; 1541]. The most prevalent OI occurring after the first OI were VZV (n=90, 22.5%), followed by *Clostridioides difficile* colitis (n=50, 12.5%), CMV disease (n=49, 12.3%), *norovirus* chronic diarrhea (n=46, 11.5%), *pneumocystis* pneumonia (n=28, 7.0%), and *BKV* nephritis (n=26, 6.5%).

Only 3 OI occurred in a median year after the first OI: “Other molds” infections (99.5 [45; 405]), *BKV* nephritis (201,5 [149; 330]), and CMV disease (354 [102; 1358]). All recurrent OI and delays are presented in Figure 6.

| Pathogen | Number of patients (%) | Median delay from first OI, days [IQR] |
|--|------------------------|--|
| Viral infections | | |
| BKV | 26 (6.5) | 201.5 [149 ; 330] |
| CMV | 49 (12.2) | 354 [102 ; 1358] |
| VZV | 90 (22.5) | 829 [407 ; 1646] |
| Kaposi | 14 (3.5) | 830.5 [231 ; 1279] |
| VHE | 10 (2.5) | 959,5 [216 ; 1571] |
| Norovirus | 46 (11.5) | 1150 [424 ; 1894] |
| HSV | 8 (2.0) | 1571 [679.5 ; 2304.5] |
| JCV | 0 | / |
| Fungal and parasitic infections | | |
| Other molds | 13 (3.2) | 122 [45 ; 405] |
| Cryptococcus | 6 (1.5) | 369.5 [181 ; 2330] |
| Pneumocystis | 28 (7.0) | 391.5 [92.5 ; 1372] |
| Microsporidium | 5 (1.3) | 419 [277 ; 623] |
| Candida | 11 (2.7) | 441 [110 ; 3668] |
| Aspergillus | 15 (3.8) | 493 [33 ; 1258] |
| Toxoplasmosis | 1 (0.3) | 680 |
| Cryptosporidium | 2 (0.5) | 1078.5 [736 ; 1421] |
| Bacterial infections | | |
| Mycobacterium TB | 8 (2.0) | 374 [134 ; 611] |
| Nocardia | 6 (1.5) | 478.5 [57 ; 1596] |
| Clostridioides difficile | 50 (12.5) | 580 [212 ; 1584] |
| Mycobacterium non TB | 9 (2.3) | 1009 [46 ; 1703] |
| Listeria | 3 (0.7) | 1298 [105 ; 2019] |

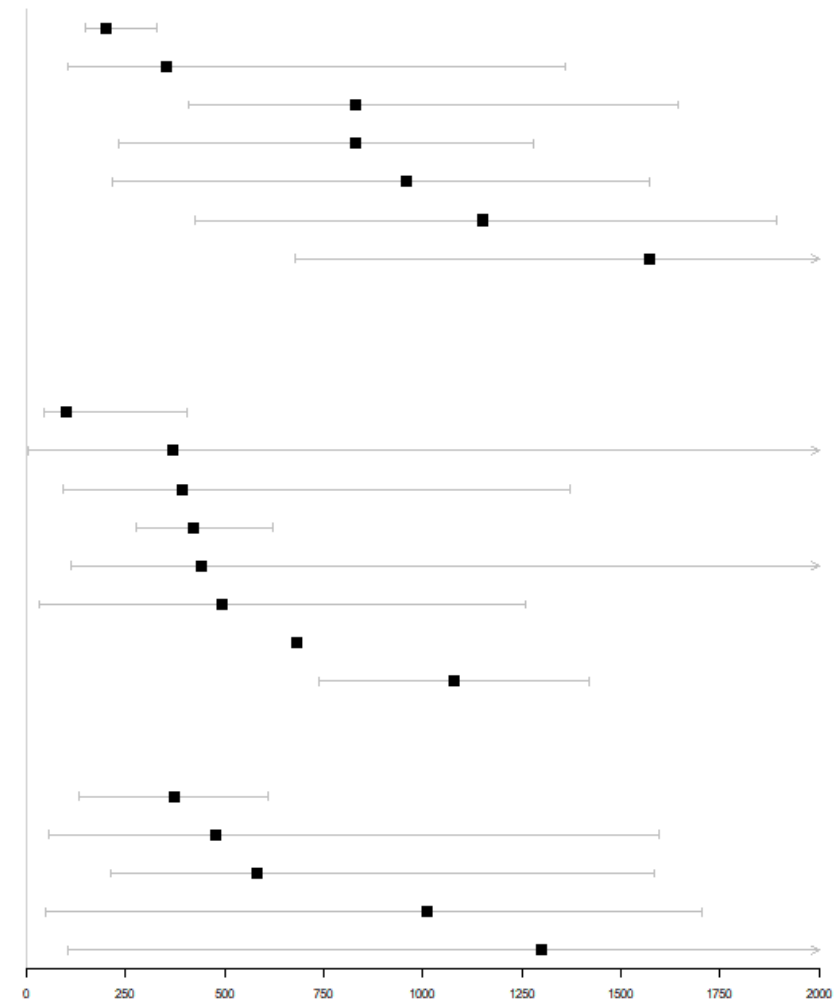


Figure 6: Description and delay of recurrent OI
Recurrent OI include all OI occurring after the first OI

3. Factors associated with multiple OI: univariate analysis

In univariate time-to-event analysis, factors associated with the recurrence of OI were recipient age (HR per 10 years increase: 1.23 (1.13-1.34), $p < 0.001$), and extended donor criteria (ECD) (HR 1.80 (1.41-2.30), $p < 0.001$). Female were associated with an increased risk for OI recurrence (HR 1.41 (1.13–1.76), $p < 0.001$) while graft rank was not associated with recurrence (HR 1.01 (0.73-1.39), $p = 0.97$). There was an association with the pretransplant CMV status of the patients as compared to the seronegative patients (D-/R-) (reference category), (D-/R+, HR 1.61 (1.01-2.56); D+/R- (HR 1.88 (1.18-2.99); D+/R+, HR 2.02 (1.30-3.14); $p = 0.007$), but there was no association with EBV ($p = 0.76$), VHC ($p = 0.36$), HIV ($p = 0.98$), HBV (0.61) pretransplantation status.

Concerning patient's medical history, there was no association of the underlying nephropathy with the recurrence of an OI ($p = 0.89$). There was an association of the pathogen of the first OI with the risk of recurrence of an OI, since *Clostridioides difficile* (HR 1.74 (1.25-2.42), $p = 0.001$) and *Candida* (HR 4.47 (1.65-12.1), $p = 0.02$) were associated with an increase of the recurrence of OI, whereas VZV infections were associated with lesser recurrences (HR 0.59 (0.43-0.80), $p < 0.001$). Induction and maintenance immunosuppressive regimens, and acute rejection episodes were not associated, excepting a slight protective trend for patients receiving ciclosporine (HR 0.78 (0.59-1.03), $p = 0.08$). Concerning time varying variables, there was an association of OI recurrence with the decrease of glomerular filtration rate (GFR) (HR 1.16 (1.09-1.25), $p < 0.001$). BMI $< 17 \text{ kg/m}^2$ tended to be associated with an increase of the risk of recurrence and a BMI higher than 30 kg/m^2 was protective for the risk of recurrence as compared to the reference category $20\text{-}25 \text{ kg/m}^2$ (HR < 17 : 1.88 (0.99-3.57); HR 17-

20: 0.92 (0.65-1.30); HR 25-30: 0.81 (0.62-1.06); HR >30: 0.65 (0.44-0.97), $p=0.04$).

Concerning post transplantation complications, several were associated such as: hematological/cytopenia (HR 1.53 (1.22-1.92), $p<0.001$), neurological (HR 1.47 (1.00-2.15), $p=0.05$), cardiac (HR 1.34 (1.07-1.68), 0.01) and especially cardiopathy (1.36 (HR 1.07-1.71), $p=0.01$), rheumatological (HR 1.33 (1.02-1.73), $p=0.03$), uro-nephrological (HR 1.87 (1.14-3.06), $p=0.02$), and venous thromboembolism (HR 1.62 (1.25-2.09), $p<0.001$).

Table 4 Factors associated with OI recurrence, univariate analysis

| Variable | effective | events | HR 95%CI | p-value |
|--|-----------|--------|-------------------------|------------------|
| Age at transplantation (HR/10 years increase) | 1802 | 322 | 1.23 (1.13-1.34) | <0.001 |
| Gender (ref=men) | 1802 | 322 | 1.41 (1.13-1.76) | 0.002 |
| Living-related donor | 1811 | 322 | 0.86 (0.63-1.17) | 0.32 |
| Graft rank | 1814 | 322 | 1.01(0.73-1.39) | 0.97 |
| Standard vs extended donor criteria | 1587 | 274 | 1.80 (1.41-2.30) | <0.001 |
| Donors Gender (ref=women) | 1811 | 322 | 0.87 (0.70-1.08) | 0.21 |
| CMV status D/R | 1732 | 306 | | 0.007 |
| -/- | | | Ref. | |
| -/+ | | | 1.62 (1.02-2.57) | |
| +/- | | | 1.87 (1.18-2.98) | |
| +/+ | | | 2.023(1.30-3.15) | |
| EBV status D/R | 1656 | 298 | | 0.76 |
| -/- | | | Ref. | |
| -/+ | | | 1.36 (0.18-10.46) | |
| +/- | | | 1.71 (0.22-13.36) | |
| +/+ | | | 1.76 (0.25-12.60) | |
| HCV status D/R | 1722 | 306 | | 0.36 |
| -/- | | | Ref. | |
| -/+ | | | 1.13 (0.67-1.91) | |
| +/- | | | 0.28 (0.04-2.00) | |
| +/+ | | | 0.57 (0.08-4.04) | |
| HIV status D/R | 1736 | 309 | | 0.98 |
| -/+ | | | 0.98 (0.31-3.07) | |
| HBV status D/R (HbS antigen) | 1795 | 319 | | 0.61 |
| -/- | | | Ref. | |
| -/+ | | | 1.20 (0.59-2.42) | |
| +/- | | | nr | |
| Induction therapy | 1801 | 322 | | 0.18 |
| Depleting induction | | | 1.46 (0.94-2.28) | |
| Non depleting induction | | | 1.46 (0.94-2.26) | |
| Initial nephropathy | 1802 | 322 | | 0.89 |
| Glomerular nephropathy | | | 0.88 (0.64-1.22) | |
| Interstitial nephropathy | | | 0.91 (0.60-1.38) | |
| Polycystic kidney disease | | | Ref. | |
| Vascular nephropathy | | | 0.92 (0.56-1.51) | |
| Diabetic nephropathy | | | 1.14 (0.72-1.82) | |
| Others | | | 0.86 (0.56-1.34) | |
| Undetermined | | | 0.84 (0.57-1.22) | |

| | | | | |
|--|------|-----|--------------------------|------------------|
| Duration of dialysis pretransplantation | 1597 | 281 | 1.00 (0.99-1.00) | 0.47 |
| Medical history | | | | |
| Dyslipidemia | 1735 | 311 | 1.07 (0.84-1.37) | 0.56 |
| High blood pressure | 1735 | 311 | 0.79 (0.59-1.06) | 0.12 |
| Neoplasia | 1735 | 311 | 1.22 (0.86-1.73) | 0.27 |
| Cardiopathy | 1735 | 311 | 1.07 (0.83-1.38) | 0.58 |
| Arteritis | 1735 | 311 | 1.16 (0.77-1.77) | 0.48 |
| Diabetes | 1735 | 311 | 1.36 (0.99-1.86) | 0.06 |
| Arrhythmia | 1735 | 311 | 1.10 (0.70-1.73) | 0.69 |
| Stroke | 1735 | 311 | 0.60 (0.27-1.35) | 0.18 |
| Disseminated infection | 1735 | 311 | 1.67 (0.98-2.83) | 0.08 |
| Kaposi | 1735 | 311 | 2.25 (0.55-9.23) | 0.26 |
| Tuberculosis | 1735 | 311 | 2.76 (1.35-5.62) | 0.02 |
| First opportunistic infection | | | | |
| <i>CMV</i> | 1802 | 322 | 1.01 (0.78-1.32) | 0.93 |
| <i>VZV</i> | 1802 | 322 | 0.59 (0.43-0.80) | <0.001 |
| <i>BKV</i> | 1802 | 322 | 0.91 (0.61-1.35) | 0.62 |
| <i>Clostridioides difficile</i> | 1802 | 322 | 1.74 (1.25-2.42) | 0.001 |
| <i>Norovirus</i> | 1802 | 322 | 1.02 (0.68-1.50) | 0.94 |
| <i>Candida</i> | 1802 | 322 | 4.47 (1.65-12.10) | 0.02 |
| <i>Pneumocystis</i> | 1802 | 322 | 0.95 (0.56-1.60) | 0.84 |
| <i>Aspergillus</i> | 1802 | 322 | 1.52 (0.90-2.56) | 0.12 |
| <i>Mycobacterium non TB/Nocardia</i> | 1802 | 322 | 1.43 (0.86-2.37) | 0.16 |
| <i>Mycobacterium tuberculosis</i> | 1802 | 322 | 1.00 (0.53-1.88) | 0.99 |
| Maintenance immunosuppressive therapy | | | | |
| Tacrolimus | 1752 | 310 | 1.15 (0.91-1.46) | 0.24 |
| Ciclosporine | 1752 | 310 | 0.78 (0.59-1.03) | 0.08 |
| Azathioprine* | 1748 | 309 | 1.38 (0.93-2.04) | 0.13 |
| Mycofenolate mofetil * | 1748 | 309 | 1.02 (0.77-1.35) | 0.88 |
| Steroids* | 1751 | 310 | 1.23 (0.85-1.77) | 0.27 |
| mTor inhibitors* | 1759 | 309 | 0.73 (0.41-1.30) | 0.28 |
| Glomerular filtration rate (HR per 10ml/minute decrease) * | 1763 | 310 | 1.16 (1.09-1.25) | <0.001 |
| BMI cat* | 1802 | 322 | | 0.04 |
| 20-25 | | | Ref. | |
| <17 | | | 1.88 (0.99-3.57) | |
| 17-20 | | | 0.92 (0.65-1.30) | |
| 25-30 | | | 0.81 (0.62-1.06) | |
| >30 | | | 0.65 (0.44-0.97) | |
| Acute rejection episode* | 1802 | 322 | 1.07 (0.84-1.35) | 0.59 |
| POST TRANSPLANT Complications* | | | | |
| Cytopenia | 1802 | 322 | 1.53 (1.22-1.92) | <0.001 |

| | | | | |
|--------------------------|------|-----|-------------------------|------------------|
| Neurologic | 1802 | 322 | 1.47 (1.00-2.16) | 0.05 |
| Vascular | 1802 | 322 | 1.20 (0.96-1.51) | 0.11 |
| Neoplasia | 1802 | 322 | 1.17 (0.91-1.49) | 0.22 |
| Rhumatologic | 1802 | 322 | 1.33 (1.02-1.73) | 0.03 |
| Pulmonary | 1802 | 322 | 1.36 (0.99-1.89) | 0.06 |
| Uro-nephrological | 1802 | 322 | 1.87 (1.14-3.06) | 0.02 |
| Diabetes | 1802 | 322 | 1.12 (0.87-1.44) | 0.38 |
| Cardiopathy | 1802 | 322 | 1.36 (1.07-1.71) | 0.01 |
| Thrombosis | 1802 | 322 | 1.62 (1.25-2.09) | <0.001 |

*Time varying variables

4. Factors associated with multiple OI: multivariate analysis

After adjusting on confounding factors, age (HR per 10 years increase: 1.21 (1.11-1.33), $p < 0.001$), female gender (HR 1.37 (1.08- 1.74)), $p = 0.009$), denutrition (HR BMI $< 17 \text{ kg/m}^2$: 2.27 (1.18- 4.38) and decreased renal function (HR per 10ml GFR decrease: 1.14 (1.05 ; 1.22), $p = 0.001$) were significantly associated with an increased risk of OI recurrence. Overweight and obesity were associated with less recurrence of OI as compared to the reference category 20-25 kg/m^2 (HR 25-30 kg/m^2 : 0.73 (0.55- 0.97); HR $> 30 \text{ kg/m}^2$: 0.50 (0.33 ; 0.76)). An history of tuberculosis pre-transplantation was associated with more recurrence of OI (HR 2.13 (1.03; 4.39), $p = 0.02$).

Concerning the first reported opportunistic infection, only *Clostridioides difficile* colitis was associated with an increased risk of recurrence of OI (HR 1.70 (1.19- 2.43), $p = 0.004$), and there was a trend for *Candida* (HR 3.06 (0.96-0.76), $p = 0.059$), whereas VZV infection was associated with less recurrence (HR 0.68 (0.48- 0.92), $p = 0.009$).

Regarding post transplant complications, cytopenia (HR 1.30 (1.02- 1.65), $p = 0.035$), and thrombosis (HR 1.47 (1.13- 1.93), $p = 0.005$) were significantly associated with recurrence of OI. The final adjusted model is reported in table 5.

Table 5: Factors associated with OI recurrence, adjusted model

| variable | HR IC95* | p-value |
|--------------------------------------|-------------------|---------|
| Age (HR per 10 year increase) | 1.21 (1.11- 1.33) | <0.001 |
| Women | 1.37 (1.08- 1.74) | 0.009 |
| GFR, MDRD (HR per 10ml/min decrease) | 1.14 (1.05-1.22) | 0.001 |
| BMI, kg/m ² | | <0.001 |
| 20-25 | Ref. | |
| <17 | 2.22 (1.15-4.28) | |
| 17-20 | 0.98 (0.68-1.42) | |
| 25-30 | 0.73 (0.55-0.97) | |
| >30 | 0.50 (0.33-0.76) | |
| First OI | | |
| VZV | 0.68 (0.49-0.94) | 0.019 |
| <i>Clostridioides difficile</i> | 1.70 (1.19-2.43) | 0.004 |
| <i>Candida</i> | 3.06 (0.96-9.67) | 0.059 |
| Complications | | |
| Cytopenia | 1.30 (1.02-1.65) | 0.035 |
| Thrombosis | 1.47 (1.13-1.93) | 0.005 |
| TB history | 2.13 (1.03-4.39) | 0.019 |

IV. DISCUSSION

Several studies investigated factors associated with the occurrence of any opportunistic infection in solid organ transplant recipients, but our study is the first to focus on the factors associated with the occurrence of multiple OI in KTR that have already presented one. This is also to our knowledge the largest published study focusing on factors associated with OI in KTR.

Among the 9752 patients included in DIVAT cohort during the study period, 1872 (19.6%) patients presented an OI according to our criteria and 334 (3.4%) presented more than one episode of opportunistic infection. In the literature, incidence of OI varies among studies between 5.5% and 12.4% depending on the population, and on the definition of included OI (36–38). OI infection risk also differs depending on the type of the transplanted organ, being less frequent in KTR than in other SOT recipients (20,36,38). Concerning the OI included in this analysis, a systematic review of all cases by an expert clinician or a trained researcher allows confidence regarding the definition of the cases included, even if it doesn't exclude underreporting of some OI.

There is up to now, no consensual definitions regarding what pathogen has to be considered as an opportunistic agent in SOT recipients. Most of the published studies refer to AIDS classifying pathogens regarding a partial common immunodepression and the absence of standardised definition referring to opportunistic pathogens in the context of SOT (54). Both populations present a predominant cellular deficiency, but SOT also present humoral deficiency (55). Furthermore, organ specificity has to be considered since patients present different specific risk, BKV nephritis in KTR being a typical example (56). In this context, there are differences regarding pathogens included or not between studies focusing on the OI in the context of SOT. *Clostridioides*

difficile is not listed as an opportunistic pathogens since its main risk factor for developing a colitis remains antimicrobial use (57). On another hand, patients background has appeared to be pivotal in the risk of occurrence, and especially of recurrence, an underlying immunitary deficiency being one the most important factors (58). We chose to include this pathogen regarding an increased incidence and a particular presentation in the context of kidney transplantation since apart prior antibiotherapy, factors such as CMV disease, acute graft rejection and hypogammaglobulinemia are associated with the occurrence of *Clostridioides difficile* colitis in KTR (59,60). On the contrary, some pathogens sometimes reported as OI, such as *Legionella* (35,61), were not included in the analysis regarding insufficiently consistent evidence for being an opportunistic pathogen. We also have to notice that we only included in our study invasive *Candida* infections and not all *Candida* infection reported in the register, which differs with data reported in the literature. Indeed, we considered that urinary tract infections and muco-cutaneous candida infections were not to be considered as OI, because they reflect more early graft and surgical complications, than immunosuppression induced infections (13), and they were likely to be underreported in our register. Anyway, all these pathogens gathered only represent a small amount as compared to *CMV*, *VZV* or *BKV*.

As expected, viral infections were the most frequent OI, followed by fungal infections and bacterial infections. At any period during 2000 and 2018, *CMV* was the most prevalent OI despite evolutive preventions and guidelines. In a recently published study using USRDS database to evaluate the impact of infections following kidney transplantation, *CMV* was, as in our study, the first OI reported. On the contrary, in the paper published by Mondor team, only 3 *CMV* disease were reported in a cohort of 588 KT(37), which is surprising. While possibly underreported in our register, *VZV* is,

as expected, a major burden after kidney transplantation (62). Long term valaciclovir prevention is not routinely recommended. In our study *Norovirus* diarrhea is very common, despite a major underreporting: Its search only became available after 2008 (23), and until recently was almost exclusively performed in Necker center. Thus it might in fact be the first cause of OI. Concerning fungal OI, despite generalized use of pneumocystosis prophylaxis in the 3-12 months following transplantation, pneumocystosis is the first cause of OI, raising the question of a more prolonged prophylaxis. Interestingly, invasive *Candida* infections were from far less common than expected (20). We cannot exclude that some late candidemia occurring just before patient's death were underreported. If we compare our results with the literature, an important attention has to be paid to the post transplant period studied. As an example, in the recently published study describing the incidence of post-transplant infections in the swiss national cohort during the first year post transplantation, *Candida* represented more than 50% of the fungal infections occurring in KTR, whereas thanks to prophylaxis, only few *Pneumocystis* pneumonia were recorded over that period. Also, these *Candida* infections included non-invasive infections (4).

Most frequent bacterial infections were *Clostridioides difficile*, followed by tuberculous and non-tuberculous mycobacteria. These results enhance the need for antibiotic stewardship in transplantation to avoid unnecessary prescription and reduce the risk of *Clostridioides*, that was recently reported to be associated with an increased risk of graft loss or death in KT recipients (5). They also raise again the question of treatment of tuberculous latent infections, which is recommended in transplant recipients.

Recurrent opportunistic infections occurred in 17.8% of the patients presenting at least an OI. Among these recurrent infections, the most prevalent OI was VZV (22.5%), followed by *Clostridioides difficile* (12.5%), CMV (12.2%), *Pneumocystis* (7.0%) and

BKV nephritis (6.5%). Regarding the heterogeneity of the recurrent OI in these patients, accurate preventive measures are difficult to consider and design. As an example, VZV, the most frequently recurrent OI will happen in 3.7% in a median delay of 829 days [407; 1646]. Should we, regarding that result, propose the use of valaciclovir in kidney transplant recipient once they present an OI? Should we propose BKV monitoring in the year following an OI, as 26/1872 patients developed BKV nephritis in a median delay of 201 days after the first OI? As a comparison, pneumocystis pneumonia incidence in the first 6 months post transplantation was around 10% in the preprophylaxis era in SOT patients (63,64). If we consider another population, a one year incidence of 20% of invasive fungal infections, mostly candidiasis, justifies a prophylaxis in liver transplant recipient (65,66). There is no consensual guideline or general principle defining when an identified risk justifies an intervention such as prophylaxis, and it depends of several parameters such as: incidence, potential severity of the infection, tolerance and performance of the available prophylaxis. As an example, until the availability of letermovir, CMV mismatch bone marrow allograft recipient did not benefit from prophylaxis regarding unacceptable haematological side effects, whereas it is commonly used in SOT recipients (67).

There was a strong association between OI recurrence and recipient's age and decrease of GFR. These factors are commonly associated with the incidence of infections in KTR (4,5). In series focusing on the incidence of OI in SOT recipients, age was not associated, but there was an increased incidence in patients receiving an ECD kidney, a proxy for older recipients (37). GFR decrease reflects different aspects of KTR including rejection episodes, recurrent urinary tract infections, patients comorbidities, complications and hospitalisations, as treatment toxicities. In non-transplant patients,

it is well proven that the infectious risk increases with GFR lowering (68,69). We could thus focus on the older patients with the worst kidney transplant function to experiment new measures of prevention.

There was an increased risk of OI associated with denutrition. Denutrition is not directly cited as a factor associated with increased infection in KTR, however it is highly connected with two notions that are associated with increased morbi-mortality: sarcopenia and frailty (70,71). Both factors are known to be associated with increased post transplantation complications including early rehospitalisation (72,73). We can thus consider that in context of SOT, a BMI <17kg/m² reflects a general debilitated status that might favour recurrent OI. We have no explanation to explain a decreased risk of infection in patients with overweight or obesity but have to notice that this association was persistent in all the sensitivity analysis that we performed.

There was an increased risk of recurrence of SOT in women. Women are known to be at increased risk for any infections in the population KTR (5). That overall increased risk mostly reflects an increased incidence of urinary tract infection in women regarding anatomic predispositions (74,75), but not only. Concerning OI, that predisposition is not able to explain gender differences. There are no existing data suggesting an increased risk of overall infectious risk in women, except during pregnancy. As women are at increased risk of HLA immunization after pregnancies (76,77), which increases the risk of rejection after kidney transplantation, we cannot exclude that their through level of immunosuppressive regimens were kept higher than those of men after transplantation, increasing their immunodeficiency. We are currently investigating this hypothesis.

Clostridioides difficile was the only pathogen significantly associated with the risk of recurrence. This information is of high value since it easily helps to identify which

patients are at particular risk of recurrence at the time of the first OI. CD occurred mostly early after transplantation (median delay 216 days [33; 1330]). This early presentation definitely increases the probability of a subsequent OI as compared to an OI that would occur after a much longer period but is not the only reason for this association. First, other OI as CMV (median delay 162 days [60; 314.5] or BK virus (median delay 267 days [130; 507]) have an early presentation, but don't increase recurrence risk. Second, in the sensitivity analysis, the association persisted even after adjusting on the time from transplantation to first OI. These facts suggest that *Clostridioides* infections happen in particularly debilitated patients, immunitary deficiency such as hypogammaglobulinemia being a known risk factor of CD (58). On the contrary, VZV was the only OI associated with less risk of recurrence. This suggests that VZV does not represent a particular warning for the risk of recurrence, but might require more specific prevention schedules, as adjuvanted recombinant zoster vaccine (78).

Venous thromboembolism (VTE) incidence is increased in chronic kidney disease and in KTR (79,80). Factors associated with venous thromboembolism in these patients are age, prolonged or recurrent hospitalisation, surgery, or prolonged bed rest (81). Those factors are enhanced in patients presenting transplantation complication leading to prolonged or recurrent hospitalisation, such as graft rejection episode (82). The association between VTE and OI recurrence might not be a causative relation, but the association of both of these conditions with a general debilitated status.

Finally, the only medical history associated with recurrence of OI was tuberculosis prior to transplantation. That association was persistent in sensitivity analysis excluding tuberculosis of the analysed OI. After a contact with *Mycobacterium tuberculosis*, it is estimated that around 10% of humans will develop a tuberculosis, and some work

suggests that all humans are not equal facing this risk (83). If mendelian mutations providing susceptibility to mycobacterial infection are extremely rare (84), polymorphism of the IL-12 and interferon gamma axis might explain partially those differences (85,86). Immunity to other OI as some fungal infections also depends on Th1 T lymphocyte activation (87), but there's no known association of predisposing risk factor for TB also exposing patients to other infections. We can nonetheless hypothesize that there might be a synergic effect of combined inherited polymorphism with the introduction of immunosuppressive regimen. Despite difficult to prove, we cannot exclude that socio-economic factors leading to enhanced risk of TB might also be responsible for increased risk of other OI. An US study tended to find an association between socio-economic level and the risk of graft rejection or the overall graft survival, in the subgroup of African American patients(88). These data should be analysed with caution and cannot easily be applied to French patients.

Our analysis suggests no association of the immunosuppressive regimen (induction or maintenance) with the risk of recurrence of OI. This result is surprising since a steroid based maintenance, or steroid based acute rejection episode regimen is commonly reported as a risk factor of OI (25,39,89). The absence of association might be explained by the absence of information regarding steroid therapy dosage, or the cumulated steroid dose, that also have an influence on OI risk (90). There was neither an association of the cumulated number of IS (1,2, or 3 different treatments as maintenance therapy) on the recurrence of OI, suggesting that immunosuppressive regimen alleviation doesn't impact the risk of recurrence. Some other factors such as an history of diabetes or post-transplant diabetes are neither associated with the risk of OI recurrence. These results might be explained by our methodological approach:

the first OI may already be a signal of major immunosuppression, possibly associated with immunosuppressive regimen and diabetes, which we are not studying here.

Our prospective register has several limits. First of them, patients have been included along a long period. Thus, there are differences over the period regarding immunosuppression, prophylaxis and screening. Knowledge and diagnosis tools for some pathogens, such as *E hepatitis* or *Norovirus*, and their particular presentation in the context of SOT have also evolved over the period resulting in paradigm changes and heterogeneity(21,22), thus they are likely to be underreported. There were also differences in data collection regarding the diagnosis of OI. For Necker center, all medical files were entirely reviewed one by one, leading to less underreporting. However, implementation of the infection database was performed in all centers by systematic microbiological laboratories and anatomo-pathological charts extractions. Prophylaxis procedure were not available at the time of the analysis, which might have changed the results of the analysis. Thus, regarding heterogeneity between centers concerning therapeutic habits and database management, analysis had to be stratified which limits the power of our analysis.

V. PERSPECTIVES

After these analyses, some points remain to be studied.

First, we would like to describe factors associated with the occurrence of the first OI in our cohort, in order to ensure that our data are comparable with the existing literature and to improve the external validity of our results. We also have to study the impact of single and multiple OI on graft and patient's survivals.

In order to discriminate the impact of the transplantation period, we plan to stratify our analysis in different periods, and especially focus our analysis on the 2008-2018 period, because data collection was improved after 2008.

We would also like to improve the characterization of the combined impact of age increase and decreased GFR on the recurrence of OI as a combined parameter.

Other aspects that we plan to consider are the potential gender differences concerning through level of IS and a potential risk of OI recurrence.

And finally, we plan to perform archetypal analysis of the recurrence patterns to distinguish infectious sequences difficult to detect with conventional inferential statistics.

VI. CONCLUSION

As a conclusion, in our prospective register study, opportunistic infections occurred in 19.6% of KTR, and were more frequent than previously described. Main OI were *CMV*, *VZV*, *BKV*, *Clostridioides difficile*, *Norovirus* and *Pneumocystis*.

Recurrent OI occurred in 334 patients, and were mainly *VZV*, *Clostridioides difficile*, *CMV*, *Norovirus*, *Pneumocystis* and *BK* virus nephropathy. Risk factors associated with OI recurrence were female gender, age, lower GFR, *Clostridioides difficile* infection as first OI, venous thrombosis, cytopenia and an history of tuberculosis before transplantation. *VZV* infection as a first OI was protective against OI recurrence compared to other OI.

More analysis and studies are required to propose personalised and highly fitted prophylaxis and prevention programs, adapted to patients' profiles.

THÈSE SOUTENUE PAR : Romain GUENEAU

TITRE :

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VU ET PERMIS D'IMPRIMER
Grenoble, le : 05/10/2020

LE DOYEN

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ANNEXE

ANNEXE 1 : LISTE DES COMPLICATIONS

| TYPE | COMPLICATION |
|-----------------------------|---|
| Appareil locomoteur | <ul style="list-style-type: none"> - Arthrite micro-cristalline ou goutte - Polyarthrite chronique (dont PR, SPA, PPR, Behcet) - Ostéoporose traitée - Ostéonécrose non infectieuse |
| Broncho-pulmonaire | <ul style="list-style-type: none"> - Affection de la plèvre et du médiastin (dont asbestose) - Asthme - Bronchite chronique, BPCO ou emphysème - Dilatation des bronches ou bronchectasie - Pneumopathie secondaire aux thérapeutiques - Mucoviscidose |
| Cardiaque | <ul style="list-style-type: none"> - Cardiopathie et cardiomyopathie ou myocardiopathie - Insuffisance cardiaque - Coronaropathie - Trouble du rythme cardiaque - Valvulopathie - Trouble de la conduction (non appareillé) - Pacemaker ou autre sonde d'entraînement - Choc (hors septique), collapsus, défaillance multiviscérale ou arrêt cardio-respi. - Hypertension artérielle pulmonaire (HTAP) |
| Chirurgical artério-veineux | <ul style="list-style-type: none"> - Pathologie artérielle du greffon avec reprise chirurgicale ou angioplastie - Thrombose artérielle partielle ou totale du transplant (+/- infarctus rénal) - Thrombose veineuse partielle ou totale - Anévrisme mycotique - Fistule artério-veineuse avec reprise chirurgicale ou angioplastie - Hémorragie du site opératoire avec transfusion ou reprise chirurgicale |
| Chirurgical urologique | <ul style="list-style-type: none"> - Sténose urétérale ou sténose urétrale - Urinome (fistule ou nécrose urétéro-vésicale) - Reflux vésico-urétéral sur le transplant avec Macroplastique ou reprise chirurgicale - Lymphocèle avec drainage ou reprise chirurgicale (marsupialisation) |

| | |
|-----------------------------|---|
| | <ul style="list-style-type: none"> - Collection nécessitant un drainage |
| Connectivite-Vascularite | <ul style="list-style-type: none"> - Microangiopathie thrombotique (sans SHU) - Cryoglobulinémie - Sarcoïdose - Autre connectivite ou vascularite (dont Churg et Strauss, Gougerot-Sjögren, périartérite noueuse ou maladie de Horton, maladie auto-immune avec ANCA) - Maladie sérique |
| Dermatologique | <ul style="list-style-type: none"> - Condylome (toute localisation) - Verrue(toute localisation) |
| Greffon pancréatique | <ul style="list-style-type: none"> - Thrombose veineuse nécessitant une reprise chirurgicale - Thrombose artérielle nécessitant une reprise chirurgicale - Thrombose veineuse partielle (veine splénique ou mésentérique) nécessitant une anticoagulation - Thrombose artérielle partielle (artère splénique ou mésentérique) nécessitant une anticoagulation - Collection péripancréatique nécessitant un drainage ou une reprise chirurgicale |
| Hématologique (hors cancer) | <ul style="list-style-type: none"> - Anémie - Leucopénie ou agranulocytose - Hémoglobinopathie - Pathologie de la coagulation (dont CIVD) - Thrombocytopénie - Gammopathie monoclonale bénigne - Pancytopénie ou aplasie - Polyglobulie |
| Hépatogastro-entérologique | <ul style="list-style-type: none"> - Ulcère oeso-gastro-duodéal - Hépatite médicamenteuse ou hépatite autre non virale - Hépatite alcoolique - Cirrhose - Lithiase vésiculaire - Cholécystectomie - Pancréatite aiguë non infectieuse - Pancréatite chronique - Polype ou adénome colique (dont sigmoïde) - Diarrhée médicamenteuse - Hypertension portale (http) (dont péliose) - Insuffisance hépato-cellulaire |

| | |
|-----------------------|---|
| | <ul style="list-style-type: none"> - Autre pathologie des voies biliaires (dont cholangite sclérosante ou maladie de Caroli) - Maladie de Crohn, rectocolite hémorragique (RCH) ou maladie coeliaque |
| Métabolique-Endocrine | <ul style="list-style-type: none"> - Diabète type I - Diabète type II - Dyslipidémie ou dyslipidémie traitée - Obésité - Parathyroïdectomie ou hyperparathyroïdectomie traitée - Affection de la thyroïde - Affection des glandes cortico-surrénales non infectieuse (dont Cushing, Addison, Conn, Phéochromocytome ou hyperplasie bilatérale des surrénales) - Diabète autre ou indéterminé |
| Néoplasique | <ul style="list-style-type: none"> - Carcinome baso-cellulaire et maladie de Bowen - Carcinome épidermoïde ou spino-cellulaire - Mélanome malin - Sarcome de Kaposi (cutané ou autre) - Cancer primitif cérébral ou neurologique - Cancer primitif ORL-stomato - Cancer primitif os-articulation-tissus mous-muscles (dont sarcomes hors Kaposi) - Cancer primitif poumon-plèvre - Cancer primitif rein - Cancer primitif voies excrétrices urinaires (dont vessie) - Cancer primitif sein - Cancer primitif gynécologique (ovaire, utérus, col) - Cancer primitif organes génitaux masculins (testicules, prostate, verge) - Cancer primitif endocrinien (hypophyse, parathyroïdes, thyroïde, surrénales) ou cancer du thymus - Cancer primitif oeso-gastro-duodéal - Cancer primitif foie-voies biliaires - Cancer primitif pancréas |

| | |
|-------------------|---|
| | <ul style="list-style-type: none"> - Cancer primitif colo-recto-anal (dont sigmoïde) - Cancer avec localisation(s) secondaire(s) ou métastase(s) - Cancer du greffon rénal ou pancréatique (hors lymphome) - Autre cancer rare (dont Merkelome) - Leucémie lymphoblastique ou myéloblastique - Lymphome ou PTLD - Myélome ou dysglobulinémie maligne (dont amylose AL) |
| Neurologique | <ul style="list-style-type: none"> - Comitialité - Encéphalopathie - Maladie neurologique dégénérative ou démence - Infirmité motrice cérébrale, retard mental ou retard psychomoteur (dont trisomie et monosomie) - Tumeur bénigne cérébrale ou neurologique - Neuropathie diabétique - Neuropathie périphérique ou polyneuropathie autre que diabétique |
| Ophthalmologique | <ul style="list-style-type: none"> - Cécité unilatérale - Cécité bilatérale - Rétinopathie liée au diabète - Cataracte - Glaucome - Rétinopathie autre que diabétique - Atteinte uvée-cornée non infectieuse |
| Psychiatrique | <ul style="list-style-type: none"> - Psychose et troubles psychotiques - Dépression sévère |
| Uro-néphrologique | <ul style="list-style-type: none"> - Néphrectomie bilatérale (reins propres) - Néphrectomie unilatérale (rein propre) - Intervention sur les voies excrétrices |
| Vasculaire | <ul style="list-style-type: none"> - Accident vasculaire cérébral - Artérite ou artériopathie - Hypertension artérielle - Maladie veineuse thrombo-embolique (MVTE) - Lymphoedème |

ANNEXE 2 : LISTE DES INFECTIONS – TYPE DE GERME

| TYPE DE GERME | NOM DU GERME |
|---------------|---|
| BACTERIE | Acinetobacter Actinomyces Anaérobie Bactéroides Bordetella (Coqueluche) Campylobacter Chlamydia Citrobacter Clostridium difficile Enterobacter Enterocoque Escherichia coli Haemophilus Helicobacter pylori Klebsiella Legionella Listeria Meningocoque Morganella Mycobactérie non tuberculeuse Mycobactérie tuberculeuse Mycoplasma ND Nocardia Pneumocoque Protéus Pseudomonas Salmonella Serratia Shigella Staphylocoque sp Streptocoque Ureaplasma |

ANNEXE 2 : LISTE DES INFECTIONS – TYPE DE GERME (suite)

| TYPE DE GERME | NOM DU GERME |
|---------------|--|
| CHAMPIGNON | Alternaria Aspergillus Candida albicans Candida non albicans Coccidioïdes Cryptocoque Fusarium Histoplasma Penicillium Pneumocystis Scedosporium Torulepsis |
| PARASITE | Amibiase Bilharziose Cryptosporidium Giardia intestinalis Leishmania Microsporidies Paludisme Toxoplasmose |
| VIRUS | Adenovirus BKv CMV EBV Enterovirus Grippe HHV6 HHV8 HIV HSV JC Virus Metapneumovirus ND Norovirus |

| | |
|--|---|
| | Parvovirus B19 Rotavirus VHA VHB VHC VHD VHE VRS VZV |
|--|---|

ANNEXE 2 : LISTE DES INFECTIONS – LOCALISATION (suite)

| LOCALISATION | TYPE D'INFECTION |
|--------------------------------------|--|
| CARDIAQUE | Endocardite Infection de prothèse valvulaire Médiastinite Myocardite Péricardite |
| CUTANE | Abcès Autre lésion Dermohypodermite Gingivostomatite Infection génitale |
| DIGESTIF | Colite Infection des voies biliaires Oesophagite ou gastrite Pancréatite Péritonite Péritonite KT de DP |
| GANGLIONNAIRE | |
| GREFFON PANCREATIQUE | Infection du liquide de conservation Pancréatite |
| GYNECOLOGIQUE | Endométrite Salpingite |
| HEMATOLOGIQUE (anémie ou leucopénie) | |
| HEPATIQUE | Abcès hépatique Hépatite |
| ND | ND |
| OCULAIRE | Kératite Rétinite Uvéite |
| ORL | Otite Sinusite |

| | |
|------------------|--|
| OSTEOARTICULAIRE | Infection de prothèse Ostéoarthrite |
|------------------|--|

ANNEXE 3 : Characteristic of the different infections.

Viral infections were the more prevalent OI since the 3 more frequent pathogens were CMV, VZV and BK virus with a total of 550 patients presenting a CMV infection. 11 of the 550 patients infected with CMV presented a recurrence of the infection, and delay of infection by CMV was 174 days [64 ; 362] after transplantation. Most of them presented an hematological infection with 276 episodes (49.3%), followed by 198 digestive infections (35.2%), 33 (5.9%) pulmonary diseases and 29 (5.2%) disseminated infections. 531 patients presented a VZV infection and 24 of them presented a recurrence. 520 patients (93.5%) presented a cutaneous infection, 13 (2.3%) presented an ophthalmic infection, 15 (2.7%) presented a CNS infection and 6 (1.1%) patients presented a disseminated VZV infection. 200 patients presented a total of 207 episodes of BK virus nephritis, and diagnosis delay was 295 days [134 ; 587]. 160 patients presented a gastro-intestinal norovirus infection and 12 of them presented a recurrence, delay between transplantation and diagnosis of the first episode was 1417 days [455,5 ; 2204,5]. The entire description of viral infections is described in table 6.

Table 6: description of viral infection

| | Number of episodes | Median time, days [IQR] |
|-------------------|-------------------------------|-------------------------|
| BKV | 200 patients (7 recurrences) | 295 [134 ; 587] |
| Nephritis | 207 (100.0) | |
| CMV | 550 patients (11 recurrences) | 174 [64 ; 362] |
| Hematological | 276 (49.3) | |
| Gastro intestinal | 198 (35.2) | |
| Pulmonary | 33 (5.9) | |
| Hepatitis | 20 (3.6) | |
| Ocular | 5 (0.9) | |
| Disseminated | 29 (5.2) | |
| Kaposi | 40 patients (4 recurrences) | 479 [245.5 ; 1055.5] |
| Cutaneous | 32 (72.7) | |
| Lymph nodes | 2 (4.6) | |
| Gastro intestinal | 1 (2.3) | |
| Hematological | 1 (2.3) | |
| Disseminated | 8 (15.0) | |
| HSV | 22 patients | 1266 [566 ; 3107] |
| Ocular | 16 (69.6) | |
| Gastro intestinal | 3 (13.0) | |
| Pulmonary | 3 (13.0) | |
| Gynecologic | 1 (4.4) | |
| JCV | 2 | 1190 [1145 ; 1235] |
| Nephritis | 2 (100.0) | |
| Norovirus | 160 patients (13 recurrences) | 1417 [455.5 ; 2204.5] |
| Gastro intestinal | 173 (100.0) | |
| VHE | 72 | 1609.5 [755.5 ; 2778.5] |
| Hepatitis | 72 (100.0) | |
| VZV | 531 patients (25 recurrences) | 791 [353 ; 1653] |
| Cutaneous | 520 (93.5) | |
| CNS | 15 (2.7) | |
| Ocular | 13 (2.3) | |
| Pulmonary | 1 (0.2) | |
| Unknown | 1 (0.2) | |
| Disseminated | 6 (1.1) | |

Bacterial infections

173 patients presented a *Clostridioides difficile* colitis and 15 of them presented a recurrence; delay of infection after kidney transplantation was 371 days [67 ; 2046]. 55 patients presented tuberculosis with a delay of diagnosis post transplantation of 629 days [228 ; 1833]. Most of them, 40 (72.7%), presented an isolated pulmonary TB infection, 3 a lymphatic infection, 2 (3.6%) a CNS infection and 5 (9.1%) presented a disseminated tuberculosis infection. 25 patients presented a non-TB mycobacterial infection, among which 9 presented a pulmonary infection and 5 presented a disseminated infection. 20 patients presented a *Nocardia* infection, mostly isolated pulmonary infection with infections. There was 5 *Listeria* infection. The entire description of bacterial infections is described in table 7.

Table 7 description of bacterial infections

| | Number of patients | Median delay, days [IQR] |
|--|----------------------|-----------------------------------|
| <i>Clostridioides difficile</i> | 173 (15 recurrences) | 371 [67 ; 1595] (premier épisode) |
| Colitis | 188 (100,0%) | |
| <i>Listeria</i> | 5 | 1795 [713 ; 2046] |
| CNS | 3 (60,0) | |
| Cutaneous | 1 (20,0) | |
| Digestive | 1 (20,0) | |
| <i>Mycobacterium non TB</i> | 25 | 1263 [425 ; 1948] |
| Pulmonary | 9 (36,0) | |
| Cutaneous | 4 (16,0) | |
| Osteoarticular | 3 (12,0) | |
| Urological | 3 (12,0) | |
| Lymph nodes | 1 (4,0) | |
| Disseminated | 5 (20,0) | |
| <i>Tuberculosis</i> | 55 | 629 [228 ; 1833] |
| Pulmonary | 40 (72,7) | |
| Lymph nodes | 3 (5,5) | |
| CNS | 2 (3,6) | |
| Cardiac | 1 (1,8) | |
| Gastro-intestinal | 1 (1,8) | |
| Gynecologic | 1 (1,8) | |
| Bone | 1 (1,8) | |
| Urologic | 1 (1,8) | |
| Disseminated | 5 (9,1) | |
| <i>Nocardia</i> | 20 patients | 557,5 [162 ; 1833,5] |
| Pulmonary | 11 (55,0) | |
| Cutaneous | 2 (8,0) | |
| Gastro-intestinal | 1 (4,0) | |
| CNS | 1 (4,0) | |
| Urological | 1 (4,0) | |
| Disseminated | 4 (20,0) | |

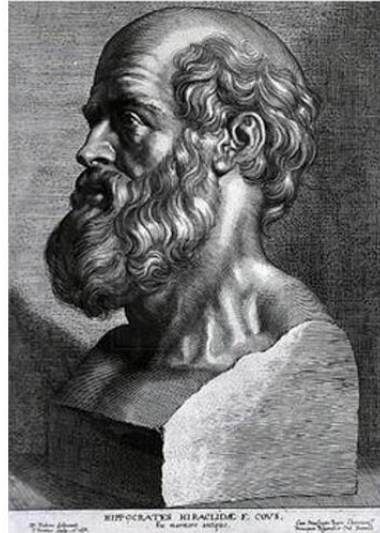
Fungal and parasitic infections

127 patients presented a pneumocystis infection with a delay of 820 days [343 ; 2362] from transplantation and a patient presented a recurrence. 91 patients presented an aspergillus infection with a median delay of 385 days [142 ; 1524]. Among patients infected with aspergillus, there was 66 (72.5%) pulmonary infections, 11 (12.1) sinusal infections and there was 6 disseminated infections (6.6%). There was 25 documented molds infection with a delay of infection of 537 days [253 ; 1368], among which 15 (60.0) cutaneous infections, 4 (16.0) pulmonary infections and 3 (12.0) vascular infections. There was 24 candida invasive infections with a delay of infection/diagnosis of 1651.5 days [435 ; 3515]. There was 12 fungemia (8.7%), 7 vascular infections (5.1%) and 4 gastro-intestinal corresponding to peritonitis. 20 cryptococcosis were diagnosed with a delay of 866.5 days [406 ; 2024.5], including 8 (40.0) CNS infections, 3 (15.0) pulmonary infections, 2 (10.0) urinary infections and there was 5 (25.0%) disseminated infections. 22 cryptosporidium infections were diagnosed with a delay of 1268.5 days [380 ; 1739]. 37 patients presented a microsporidium infection with a delay of 945 days [479 ; 1429], and 2 of them presented a recurrence. 4 patients presented a pulmonary *Mucorales* infection with a delay of 408 days [350.5 ; 2362]. And concerning parasitic infections, 7 patients were diagnosed with toxoplasmosis with a delay of 718 days [27 ; 1763], among which 5 hematological toxoplasmosis (71.4%), 1 retinitis and 1 CNS infection. The entire description of bacterial infections is described in table 8.

Table 8 description of fungal and parasitic infections

| | Number of patients | Median delay, days [IQR] |
|-------------------------------|--------------------|--------------------------|
| <i>Aspergillus</i> | 91 | 385 [142 ; 1524] |
| Pulmonary | 66 (72.5) | |
| ORL | 11 (12.1) | |
| Cutaneous | 2 (2.2) | |
| Urological | 2 (2.2) | |
| Vascular | 2 (2.2) | |
| CNS | 1 (1.1) | |
| Ocular | 1 (1.1) | |
| Disseminated | 6 (6.6) | |
| Other molds | 25 | 537 [253 ; 1368] |
| Cutaneous | 15 (60.0) | |
| Pulmonary | 4 (16.0) | |
| Vascular | 3 (12.0) | |
| ORL | 1 (4.0) | |
| Bone | 1 (4.0) | |
| Urological | 1 (4.0) | |
| <i>Candida</i> | 24 | 1651.5 [435 ; 3515] |
| Fungemia | 11 (45.8) | |
| Vascular | 7 (29.2) | |
| Gastro-intestinal | 4 (16.7) | |
| Bone | 1 (4.2) | |
| Disseminated | 1 (4.2) | |
| <i>Cryptococcus</i> | 20 | 866.5 [406 ; 2024.5] |
| CNS | 8 (40.0) | |
| Pulmonary | 3 (15.0) | |
| Urological | 2 (10.0) | |
| Lymph nodes | 1 (5.0) | |
| Isolated fungemia | 1 (5.0) | |
| Disseminated infection | 5 (25.0) | |
| <i>Cryptosporidium</i> | 22 | 1268.5 [380 ; 1739] |
| Gastro-intestinal | 22 (100.0) | |
| <i>Microsporidium</i> | 37 (2 recurrences) | 945 [479 ; 1429] |
| Gastro-intestinal | 39 (100.0) | |
| <i>Mucormycosis</i> | 4 | 408 [350.5 ; 1310.5] |
| Pulmonary | 4 (100.0) | |
| <i>Pneumocystis</i> | 127 (1 recurrence) | 820 [343 ; 2362] |
| Pulmonary | 128 (100.0) | |
| <i>Toxoplasmosis</i> | 7 | 718 [27 ; 1763] |
| Hematological | 5 (71.4) | |
| Ocular | 1 (14.3) | |
| CNS | 1 (14.3) | |

SERMENT D'HIPPOCRATE



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

