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THESE POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE

# Évaluation du traitement de première intention du reflux vésico-urétéral par injection endoscopique de polydimethylsiloxane chez 103 transplantés rénaux en prévention des récidives de pyélonéphrites aigues du greffon

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# AVERTISSEMENT

**La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteur(e)s.**

## LISTE DES ABRÉVIATIONS

IEP : Injection endoscopique de polydimethylsiloxane

IRC : Insuffisance rénale chronique

HR : Hazard ratio

PDMS : Polydimethylsiloxane = Macroplastique®

PNAG : Pyélonéphrite aiguë du greffon

RVU : Reflux vésico-urétéral

UCRM : Urétrocystographie rétrograde et mictionnelle

## LIST OF ABBREVIATIONS

AGPN : Acute graft pyelonephritis

EPI : Endoscopic polydimethylsiloxane injection

HR : Hazard ratio

PDMS : Polydimethylsiloxane = Macroplastique®

UVA : Ureterovesical anastomosis

VCUG : Voiding cystourethrography

VUR : Vesicoureteral reflux

# TABLES DES MATIÈRES

# RÉSUMÉ

**Objectif :** Le reflux vésico-urétéral (RVU) sur transplant rénal peut favoriser les pyélonéphrites aiguës du greffon (PNAG) et mettre en péril sa survie. La prise en charge chirurgicale de ce RVU par réimplantation chirurgicale ouverte est le gold standard mais est associée à une morbidité pouvant conduire également à la perte du greffon. L'objectif de cette étude était d'évaluer l'efficacité de l'injection endoscopique de polydimethylsiloxane (IEP) sur la prévention des récidives de PNAG associées à un RVU.

**Matériels et méthodes :** Une étude monocentrique rétrospective a été conduite de janvier 2000 à décembre 2017. Tous les patients ayant eu une PNAG associée à un RVU et traités en première intention par IEP ont été inclus. Le RVU était diagnostiqué et classé en bas ou haut grade par urétrocystographie rétrograde et mictionnelle. L'efficacité de l'IEP était jugée sur la récidive ou non de PNAG.

**Résultats :** 103 patients ont été inclus sur 1811 transplantations rénales. 44% avaient un RVU de bas grade et 56% de haut grade. La prise en charge endoscopique était un succès dans 59,2% des cas avec un suivi médian de 43 mois. Il n'y avait pas de différence en fonction du grade du RVU. Les facteurs de risque d'échec de l'IEP en analyse multivariée étaient l'absence de diurèse résiduelle avant la greffe rénale (*HR* 2,4; *p*=0,001), la survenue de PNAG précocement après la transplantation (*HR* 2,1; *p*=0,020) et la greffe en fosse iliaque gauche (*HR* 2; *p*=0,047). L'échec de l'IEP était de 100% lorsque les patients présentaient ces 3 facteurs de risque. Parmi les patients ayant eu un échec d'IEP, un traitement de deuxième ligne par nouvelle IEP ou réimplantation chirurgicale ouverte a été efficace dans respectivement 80% et 81,2% des cas. Aucun effet secondaire grave n'a été constaté après cette prise en charge de première ligne

**Conclusion :** Le traitement du RVU par IEP est un traitement mini invasif, efficace, facile de réalisation, de faible morbidité et de coût réduit, justifiant son utilisation en première intention dans la prévention des récidives de PNAG. Toutefois la chirurgie classique par réimplantation chirurgicale ouverte paraît plus adaptée lorsque tous les facteurs de risque d'échec de l'IEP sont réunis.

# INTRODUCTION GÉNÉRALE

## ÉPIDÉMIOLOGIE

L'insuffisance rénale chronique (IRC), définie par une clairance de la créatinine inférieure à 60ml/min/1,73m$^2$, est un problème de santé publique avec aujourd'hui 10% de la population générale atteinte(1). Son évolution naturelle tend vers l'insuffisance rénale chronique terminale et nécessite alors l'instauration d'un traitement de suppléance par hémodialyse / dialyse péritonéale ou transplantation rénale. La transplantation rénale offre de nombreux avantages par rapport à la dialyse : amélioration de la qualité de vie des patients mais également de leur espérance de vie (2)(3). Enfin, dans un système de santé rongé par ses difficultés économiques, la transplantation rénale est indiscutablement le choix de prédilection par rapport à la dialyse puisque passée la 1$^{er}$ année post transplantation, elle devient 10 fois moins coûteuse que la dialyse(1).

Malgré ces nombreux avantages l'accès à la greffe rénale reste difficile, principalement en raison d'une inadéquation entre la demande et l'offre de greffons rénaux. On retrouvait ainsi en 2016, 4,9 candidats à une transplantation rénale pour un greffon attribuable(1). Cette difficulté d'accessibilité à la greffe rénale ne cesse de s'aggraver car l'incidence de l'IRC augmente tous les ans du fait de l'allongement de l'espérance de vie, combinée à l'augmentation de l'incidence du diabète(1). Enfin, en raison du vieillissement de la population et d'une médiane de survie globale du transplant rénal de 168,6 mois, un patient déjà transplanté sera probablement candidat à une seconde greffe(4). La survie du greffon, une fois transplanté, apparaît donc comme une priorité absolue dans le contexte de pénurie d'organe.

## REFLUX VÉSICO-URÉTÉRAL

Lors de la transplantation rénale après anastomose des vaisseaux du greffon, une anastomose urétérovésicale est réalisée entre la vessie du receveur et l'uretère du greffon. Au moins 3 techniques d'anastomose urinaire existent : la réimplantation extravésicale type Lich-Gregoir, la réimplantation intravésicale type Politano-Leadbetter et la réimplantation directe de l'uretère type U-stitch(5)(6). Cette dernière n'étant pas associée à un système anti-reflux, elle est en général abandonnée au profit des 2 premières. Cette anastomose urinaire est la deuxième cause de complications postopératoires après les complications vasculaires(7). On retrouve parmi ces complications urologiques le reflux vésico-urétéral (RVU). L'incidence de ce RVU, estimée entre 1 et 86%, est très variable d'une étude à l'autre(8) car les taux de RVU diffèrent selon la technique de réimplantation urétérovésicale réalisée(9) et surtout la recherche de ce RVU n'est pas systématique. Au-delà du nombre exact de RVU post transplantation rénale, la question primordiale et toujours débattue est l'influence réelle de ce RVU sur le fonctionnement et la survie du greffon. Autrement dit, le RVU est-il un facteur de risque d'altération ou de perte du greffon et par extension, de retour en dialyse ? Selon certaines études, le RVU n'aurait pas d'effet sur la fonction rénale, la survie du greffon ni même la fréquence des infections urinaires (10)(11)(12)(13)(14)(15)(16) alors qu'au contraire d'autres soutiennent que le RVU pourrait avoir un impact sur la survie du greffon(17)(18)(19)(20)(21)(22).

Le lien de causalité entre RVU et pyélonéphrite aiguë du greffon (PNAG) reste controversé(23) et la même dualité persiste entre un effet négatif des PNAG(24)(25)(26)(27) sur le greffon et l'absence d'effet sur le greffon(28)(29).

En l'absence de consensus à propos de son impact sur le greffon, le RVU n'est pas recherché de manière systématique après une transplantation rénale(30). Néanmoins, en cas d'infection aiguë du greffon type PNAG, une recherche par urétrocystographie rétrograde et mictionnelle (UCRM) est réalisée. Si le RVU est objectivé radiologiquement, il parait nécessaire de le traiter

en raison de son potentiel effet délétère sur le greffon, d'autant plus lorsque les PNAG sont récidivantes. Des recommandations sur la prise en charge du reflux sur greffon existent, néanmoins, elles sont pour le moment basées sur des niveaux de preuve relativement faibles.(8)

## PRISE EN CHARGE DU REFLUX VÉSICO-URÉTÉRAL DU GREFFON

Le traitement de référence du RVU est actuellement la réimplantation chirurgicale ouverte qui offre d'excellents résultats (83-100%)(31)(32)(33). Cette anastomose peut être intravésicale type Politano-Leadbetter ou peut être de type pyélo-urétérale en anastomosant l'uretère natif homolatéral au pyélon du greffon. Le choix de la technique est dépendant de l'expérience du chirurgien, mais également de la qualité de l'uretère natif qui, en cas d'anomalie (sténose, reflux…), empêche son utilisation pour une réimplantation pyélo-urétérale. Eu égard aux conditions dans lesquelles cette réimplantation chirurgicale ouverte est réalisée, à savoir des tissus cicatriciels et fibrotiques secondaires à la première transplantation, cette prise en charge s'avère souvent techniquement difficile(34). Ainsi la réimplantation chirurgicale ouverte bien qu'indéniablement efficace est associée à une morbidité non négligeable (16-53%) pouvant aller jusqu'à des complications nécessitant à terme une transplantectomie du greffon(35)(36) et nécessitant de ce fait, une surveillance hospitalière prolongée en post opératoire(7)(36).

L'alternative est le traitement endoscopique par injection de matériel synthétique dans le muscle vésical à la périphérie du méat urétéral de l'uretère refluant. Cette technique consiste à modifier l'anatomie de la jonction urétérovésicale, en surélevant le plancher du méat urétéral, tentant ainsi de recréer une valve anti-reflux. Ce traitement a maintes fois prouvé son efficacité dans les reflux vésico-urétéraux sur uretères natifs, aussi bien dans les populations pédiatriques qu'adultes (37)(38) néanmoins son utilisation dans des RVU post transplantation rénale est encore limitée probablement à cause d'un nombre faible de publications sur cette technique mais aussi parce qu'il existe à ce jour plusieurs biomatériaux sur le marché, ajoutant ainsi un peu plus confusion

quant à l'utilisation de cette technique.

Les 3 principaux biomatériaux utilisés comme agent de comblement sont : le dextranomère et acide hyaluronique (Deflux®), le polymère de tétra-fluoro-éthylène (Téflon®) et le polydimethylsiloxane (Macroplastique®).

Le dextranomère semble avoir des résultats intéressants néanmoins les publications sur son efficacité sont pour le moment limitées(39)(40)(41), quant au tétra-fluoro-éthylène, il présente sur le long terme l'inconvénient d'être associé à une migration du produit et à des réactions inflammatoires locales(42)(43)(44), il n'est actuellement plus utilisé en France(45).

Le Macroplastique® est constitué de particules solides de polydimethylsiloxane (PDMS) de tailles comprises entre 80 et 450 µm diminuant ainsi son potentiel migratoire(46). De plus, aucun effet secondaire important n'a été révélé après son utilisation(47) ce qui en fait potentiellement un bon produit de comblement des RVU post transplantation rénale.

Enfin, une alternative au traitement chirurgical et endoscopique existe, il s'agit de la mise sous antibioprophylaxie au long cours. Néanmoins, il y a un risque d'émergence d'infections urinaires résistantes aux antibiotiques, qui plus est chez des patients immunodéprimés, ce qui rend ce traitement obsolète quand une prise en charge chirurgicale ou endoscopique est possible(48)(49)(50).

## OBJECTIF

L'objectif de cette étude était donc d'évaluer l'efficacité de l'injection endoscopique de polydimethylsiloxane (IEP) sur la prévention des récidives de PNAG associées à un RVU.

L'objectif secondaire de cette étude était d'identifier les facteurs de risque d'échec de ce traitement endoscopique afin de proposer d'emblée une prise en charge plus adéquate.

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# ARTICLE

## Endoscopic polydimethylsiloxane injection as an upfront treatment of vesicoureteral reflux for prevention of recurrent acute graft pyelonephritis in 103 renal transplant recipients

*Projet de publication*

# ABSTRACT

**Objectives:** Acute graft pyelonephritis (AGPN) secondary to vesicoureteral reflux (VUR) may lead to graft loss. Currently, the gold standard treatment is open surgical re-implantation but it's associated at a potential high perioperative morbidity. Other managements like endoscopic treatments exist but are underused by lack of data supporting their efficiency. The aim of this study was to evaluate the endoscopic polydimethylsiloxane injection (EPI) as an upfront treatment for VUR following renal transplantation in order to prevent recurrent AGPN.

**Methods:** A monocentric retrospective study was performed between 2000 and 2017. All patients with VUR associated to AGPN managed by EPI as an upfront treatment were included. VUR were clustered as low and high grade using voiding cystourethrography. AGPN relapse after EPI was considered as a treatment failure.

**Results:** 103 patients were included. Of these, 56% had a high grade VUR. EPI was successful in 59,2% of cases based on 43 months of follow up data. There was no difference between low and high grade VUR. In multivariate analysis, absence of residual diuresis (HR 2,4, p=0,001), early AGPN post transplantation (HR 2,1, p=0,020), and renal transplantation in left side (HR 2, p=0,047) were associated to a failure of EPI. Patients with all of these risk factors had 100% occurrence of EPI treatment failure. Among patients in failure, a new EPI or an open surgical re-implantation was efficient in respectively 80% and 81,2%. No serious adverse effects were associated with EPI.

**Conclusion:** EPI is a suitable management of VUR after renal transplantation. It has advantages in being quick, secure, minimally-invasive, and low cost. Thus, endoscopic management should be used in the first line of treatment to prevent recurrent AGPN secondary to VUR. However, open surgical re-implantation remains a good indicator if a patient is positive for all risk factors for EPI failure.

## INTRODUCTION

Urologic complications are the second most common major adverse effects in renal transplantations after vascular problems(1). Among these urologic complications, vesicoureteral reflux (VUR) is diagnosed in 1% to 86% of renal transplantations(2). The potential association of VUR with acute graft pyelonephritis (AGPN) and its effects on graft survival is still controversial. While some studies reject this link(3)(4)(5), others show that VUR and AGPN increase the risk of graft loss(6)(7)(8) especially when it occurs precociously after the transplantation(9)(10). Thus, even if the answer to this question remains unclear, if there are doubts about graft survival, patients with AGPN associated with VUR should be managed with the aim to prevent the risk of graft loss. This is especially important in a context of organ shortage.

Currently, the gold standard treatment is open surgical re-implantation which has an interesting success rate (83-100%)(11)(12)(13) but can have a high perioperative morbidity (16-53%) potentially leading, in severe cases, to nephrectomy(11)(14)(15).

Endoscopic treatment by bulking agent injection is an alternative treatment that could be used. This approach is known to be a non-invasive and effective therapy in patients with native VUR (16)(17) however it remains underutilized as upfront treatment for VUR post renal transplantation. Finally, long-term antibiotic prophylaxis is a third treatment option; however, this option seems to increase the rate of bacterial resistance, especially in an immunosuppressed patient(18).

The aim of this study was to evaluate the endoscopic polydimethylsiloxane injection (EPI) as an upfront treatment for vesicoureteral reflux post renal transplantation in order to prevent recurrent AGPN. The secondary goal was to identify risk factors for failure of this management.

## METHODS

### *Patient cohort:*

This study was monocentric using retrospective data collected from 1811 kidney transplantations between January 2000 and December 2017 from Lille University Hospital. Patients were included after at least one AGPN associated with VUR, regardless of the grade of VUR. A minimum of three months follow up was required for patient inclusion criteria. Patients who had a pyeloureteral re-implantation during the renal transplantation were excluded.

AGPN was defined by the association between fever >38 °C, positive urine culture (colony count> 10^4 UFC/mL), and an increase of creatinine relative to an individual base level of creatinine.

VUR were detected using voiding cystourethrography (VCUG) and classified by a uro-radiologist according to the International Reflux Study Committee Scale(19) (**Annexe 1**). Reflux Grade 1 and 2 were clustered as low grades while, reflux grade 3, 4 and 5 were classified as high grades.

### *Transplantation and endoscopic procedure:*

Renal transplantations were conducted by multiple surgeons. Ureterovesical anastomosis was made by Lich-Gregoir technique. The implementation of a double J catheter was variable according to the surgeon.

Concerning the endoscopic procedure, all patients had sterile urine culture before the procedure. The bulking agent used for all the procedures was a polydimethylsiloxane (Macroplastique®), which was injected through rigid cystoscopy with an adjustable needle. Injection of the bulking agent could be achieved in several points around the ureteral orifice up to a good obstruction aspect of this one.

### *Monitoring after endoscopic treatment:*

Three months after the endoscopic management, each patient was reviewed by a urologist and

had an annual consultation with a nephrologist. This management approach was considered as a failure if the patient had a new AGPN. Therefore, the success of this management was solely clinical and patients did not have a systematic control VCUG in the absence of AGPN relapse. In cases of recurrence of AGPN, a VCUG was performed again in order to objectify the failure of endoscopic treatment through remaining reflux. Therefore, a new EPI or an open surgical re-implantation was performed as a second line treatment.

***Statistical analysis:***

Categorical variables were expressed as frequency or percentage. Quantitative variables were expressed as means and standard deviations or medians and interquartile ranges. Normality of distribution was checked graphically and using Shapiro Wilk test.

The failure rate of endoscopic treatment was estimated by Kaplan-Meier analysis. The Cox proportional hazard regression was performed to estimate the risk factors of failure. The relevant risk factors statistically significant ($p$<0.05) in univariate analysis and with less than 10% missing data were introduced in multivariate analysis. A Wilcoxon signed rank test was used to compare the rate of AGPN before and after endoscopic treatment, and the paired Student t-test was used to compare the creatinine level before and after endoscopic treatment. All statistical analysis was done with SAS software (SAS Institute version 9.4).

## RESULTS

***Cohort characteristics:***

Out of 1811 renal transplantations, 103 patients were included (5,7%). They were all managed initially with EPI. The median time between transplantation and the first AGPN was 16 months and time between VUR diagnosis and endoscopic treatment was 3,5 months. Patients had a low-grade VUR and high-grade VUR in respectively 39,8% and 50,5% of cases (grade was unknown

for 10 patients). Etiologies of chronic kidney disease are presented in **Figure I** and demographic characteristics of the population in **Table I**.

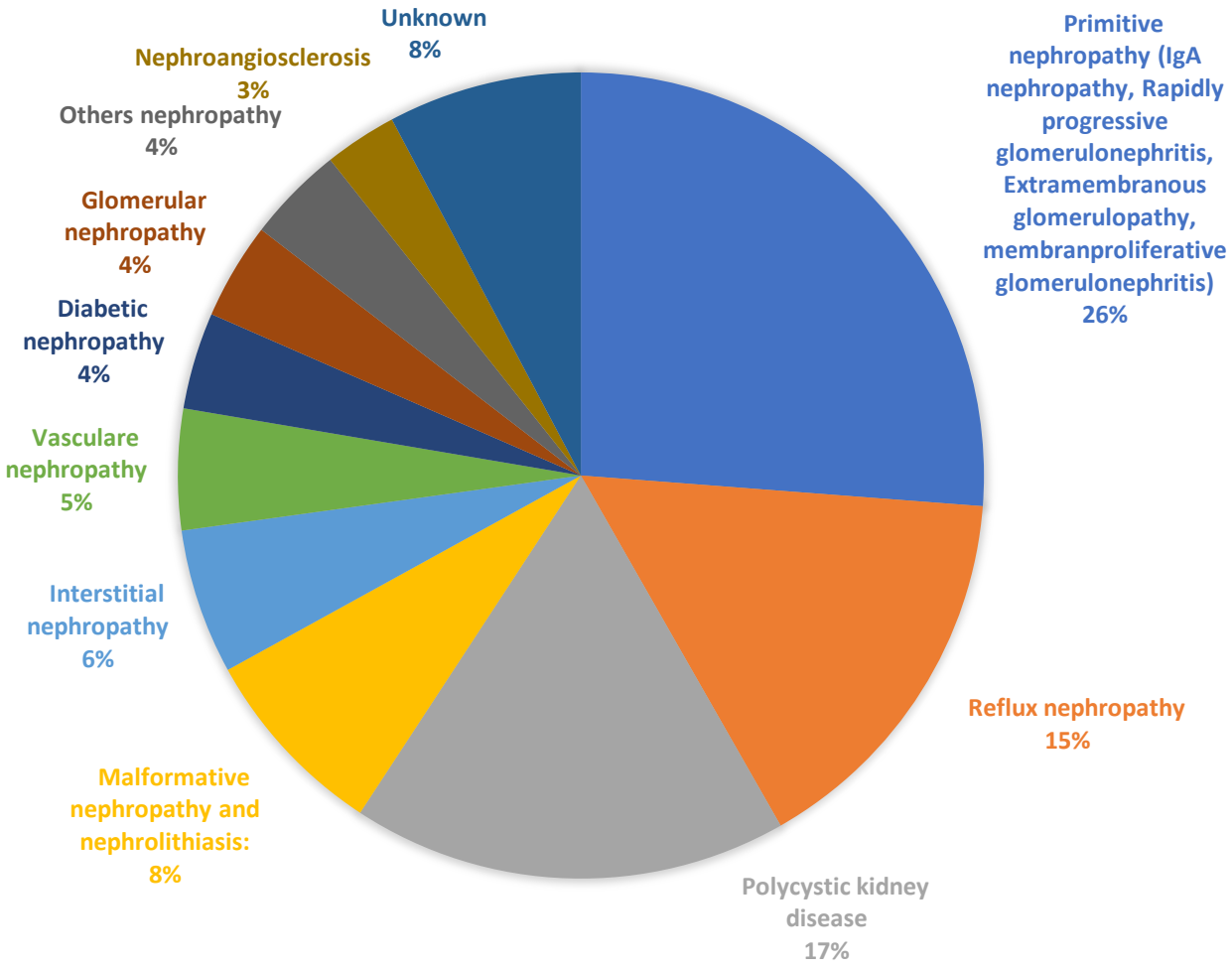


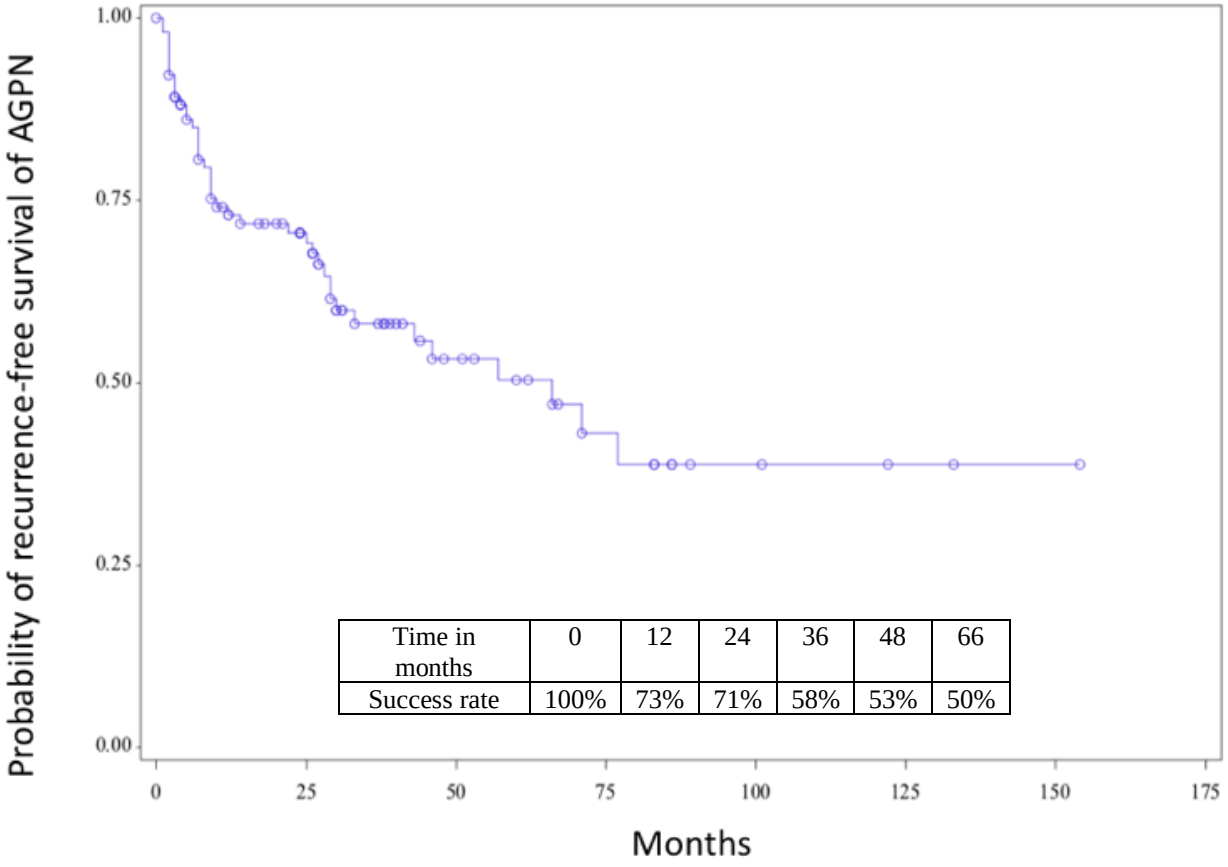

**Figure I: Etiologies of chronic kidney disease in 103 renal transplant recipients**

| | |
|---|---|
| **Population** | |
| **Gender, n (%):** Female / Male | 82 (79,6) / 21 (20,4) |
| **Residual diuresis (>400cc/days), n (%):** Yes / No | 64 (66) / 33 (34) |
| **Impaired bladder emptying, n (%):** Yes / No | 9 (8,8) / 93 (91,2) |
| **Native reflux, n (%)** | 24 (23,3) |
| **Median time in dialysis (min – max) (months)** | 23 (0 – 190) |
| **Antecedent of bladder surgery, n (%):** Yes / No | 34 (34,3) / 65 (65,7) |
| **Transplantation:** | |
| **Median age of transplantation (min - max) (years)** | 45 (10 – 76) |
| **First renal transplantation, n (%):** Yes / No | 79 (77) / 24 (23) |
| **Graft type, n (%):** | |
| Cadaveric | 96 (93,2) |
| Live | 7 (6,8) |
| **Side of transplantation, n (%):** | |
| Right | 77 (75) |
| Left | 26 (25) |
| **Quality of the bladder wall, n (%)** | |
| Normal | 54 (52,4) |
| Low | 17 (16,5) |
| Unknown | 32 (31,1) |
| **Ureteral stent, n (%):** Yes / No | 55 (56,7) / 42 (43,3) |
| **Voiding cystourethrography:** | |
| **VUR grade, n (%)** | |
| Grade 1 | 8 (7,8) |
| Grade 2 | 33 (32) |
| Grade 3 | 38 (36,9) |
| Grade 4 | 13 (12,6) |
| Grade 5 | 1 (1) |
| Unknown | 10 (9,7) |
| **VUR grade, n (%)** | |
| Low grade | 41 (39,8) |
| High grade | 52 (50,5) |
| Unknown | 10 (9,7) |
| **VUR in native ureter, n (%):** Yes / No | 11 (11,7) / 83 (88,3) |
| **Acute graft pyelonephritis:** | |
| **Median number of AGPN before the endoscopic management (min – max)** | 3 (0 – 6) |
| **Median time between the renal transplantation and AGPN (min – max) (months)** | 16 (0 – 218) |
| **Early AGPN after renal transplantation (<6months), n (%):** Yes / No | 37 (35,9) / 66 (64,1) |
| **Endoscopic management:** | |
| **Median age of endoscopic management (min - max) (years)** | 50 (23 – 79) |
| **Median time between VCUG and endoscopic management (min – max) (months)** | 3,5 (1 – 32) |
| **Median time between transplantation and endoscopic management (min – max) (months)** | 35 (3 – 222) |
| **Median quantity of Macroplastique® used, (min – max) (mL)** | 2,5 (1,5 – 5) |
| **Median follow up after the first line of treatment (min – max)** | 43 (3 – 156) |

**Table I: Demographic characteristics of the population**

***Success or failure of the endoscopic management:***

After EPI, the median follow up was 43 months (range= 3-156). 59,2% of patients had a clinical success. Median time for recurrence-free survival of AGPN after EPI was 66 months as depicted by the Kaplan-Meier plot in **Figure II**.




| Time in months | 0 | 12 | 24 | 36 | 48 | 66 |
|---|---|---|---|---|---|---|
| Success rate | 100% | 73% | 71% | 58% | 53% | 50% |

**Figure II: Recurrence-free survival of AGPN after endoscopic treatment**

Among 42 patients with a recurrence of AGPN after EPI and classified as a failure of Macroplastique®, 7 patients had a radiological success of this management with no remaining VUR. Five of these 42 patients considered as failure didn't have a radiologic control. Mean rate of AGPN in all patient was 1,57 per year per patient before the EPI and 0,23 per year per patient after the procedure ($p$<0,001).

Twenty-six patients underwent a second line treatment: 10 had a new EPI with 80% of success and 16, a pyeloureteral re-implantation with 81, 2 % of success.

***Morbidity of the endoscopic management:***

In 87% of cases, EPI was performed in outpatient surgery. Concerning the morbidity, there was no significant difference in measurable creatinine level before and after the procedure (16.0 ± 5.8 vs 16 ± 6.2) (*p*=0,963). Four patients had complications: two had a temporary obstruction which was resolved after a period of symptomatic treatment by percutaneous nephrostomy then temporary ureteral stent and two patients had a gross hematuria needing a bladder catheter up to resolution. Six patients had a graft loss during the study period without any imputation of bulking agent responsibility.

***Risk factors for failures of endoscopic treatment in first line***

As shown in **Table II**, residual diuresis (*p*=0,012), side of transplantation (*p*=0,022), rank of transplantation (*p*=0,045), early AGPN after transplantation (*p*=0,028) and quality of the bladder wall (*p*=0,036) were significantly associated with a risk of EPI failure in univariate analysis. Recurrence-free survival of AGPN based on previous risk factors is shown in **Figure III**, **IV**, **V**, **VI**, and **VII**. The grade of VUR was not associated with a risk of EPI failure (**Figure VIII**), similar than the quantity of bulking agent used or the number of injection site of polydimethylsiloxane.

| **Variables** | **Risk of AGPN recurrence after endoscopic management** |
|---|---|
| | **Hazard ratio (IC 95%); *p*** |
| **Population** | |
| **Gender: Male** | 1,110 (0,510-2,415); 0,793 |
| **Absence of Residual diuresis (<400cc/days)** | 2,262 (1,198-4,270); **0,012** |
| **Impaired bladder emptying** | 1,255 (0,445-3,541); 0,668 |
| **Native reflux** | 0,681 (0,324-1,430); 0,310 |
| **Time in dialysis (per six months increase)** | 1,010 (0,961-1,061); 0,705 |
| **Antecedent of bladder surgery** | 1,686 (0,909-3,128); 0,097 |
| **Transplantation:** | |
| **Age of transplantation (per ten years increase)** | 1,028 (0,821-1,287); 0,809 |
| **More than one renal transplantation** | 1,961 (1,016-3,785); **0,045** |
| **Graft type:** Live | 0,974 (0,300-3,158); 0,964 |
| **Renal transplantation on the left side** | 2,144 (1,118-4,113); **0,022** |
| **Low quality of the bladder wall** | 2,315 (1,058-5,067); **0,036** |
| **Presence of ureteral stent** | 1,518 (0,793-2,904); 0,208 |
| **Voiding cystourethrography:** | |
| **VUR low grade** | 0,802 (0,417-1,543); 0,509 |
| **VUR in native ureter** | 3,573 (0,853-14,971); 0,081 |
| **Acute graft pyelonephritis:** | |
| **Number of AGPN before the endoscopic management > 1** | 2,338 (0,564-9,692); 0,242 |
| **Early AGPN after renal transplantation (<6months)** | 1,979 (1,078-3,634); **0,028** |
| **Endoscopic management:** | |
| **Surgeon without experience of endoscopic management** | 1,140 (0,537-2,420); 0,734 |
| **Age of endoscopic management (per ten years increase)** | 0,964 (0,762-1,221); 0,763 |
| **Time between VCUG and endoscopic management (per six months increase)** | 0,596 (0,235-1,512); 0,276 |
| **Time between transplantation and endoscopic management (per one year increase)** | 0,907 (0,813-1,012); 0,082 |
| **Quantity of polydimethylsiloxane used (mL)** | 1,301 (0,769-2,203); 0,327 |
| **Number of polydimethylsiloxane injection site** | 0,866 (0,504-1,487); 0,601 |

**Table II: Univariate analysis of the failure factors of endoscopic management**

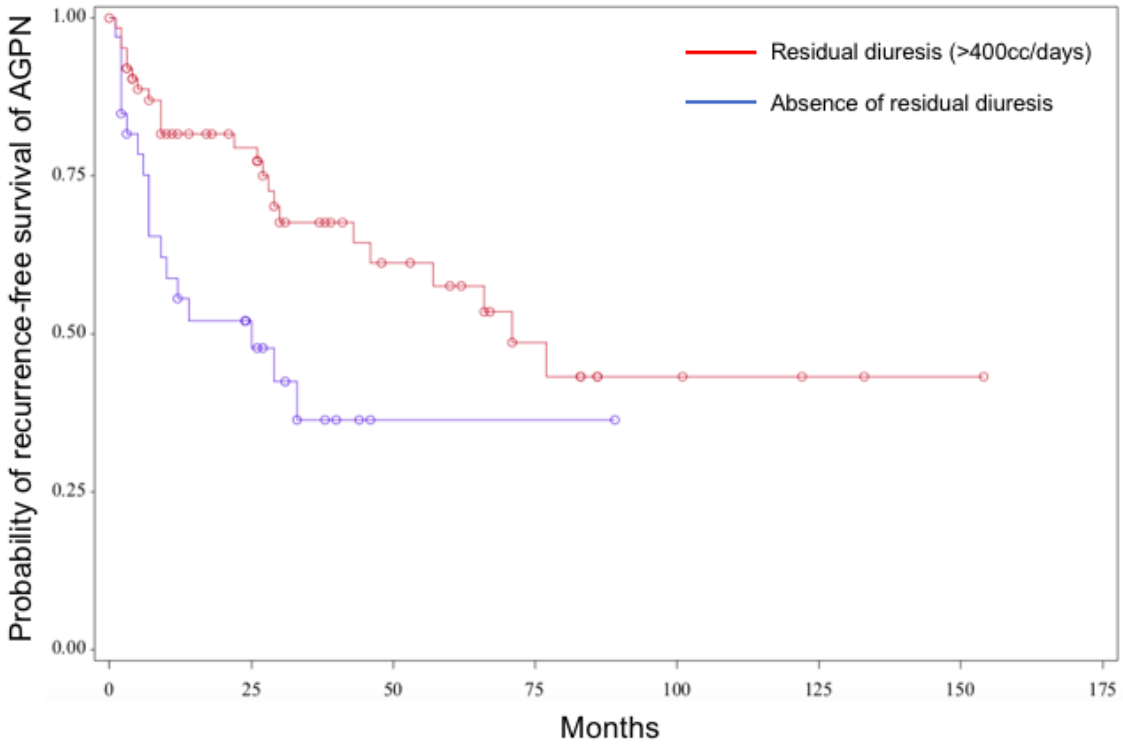



**Figure III: Recurrence-free survival of AGPN after EPI according to residual diuresis (*p*= 0,012)**

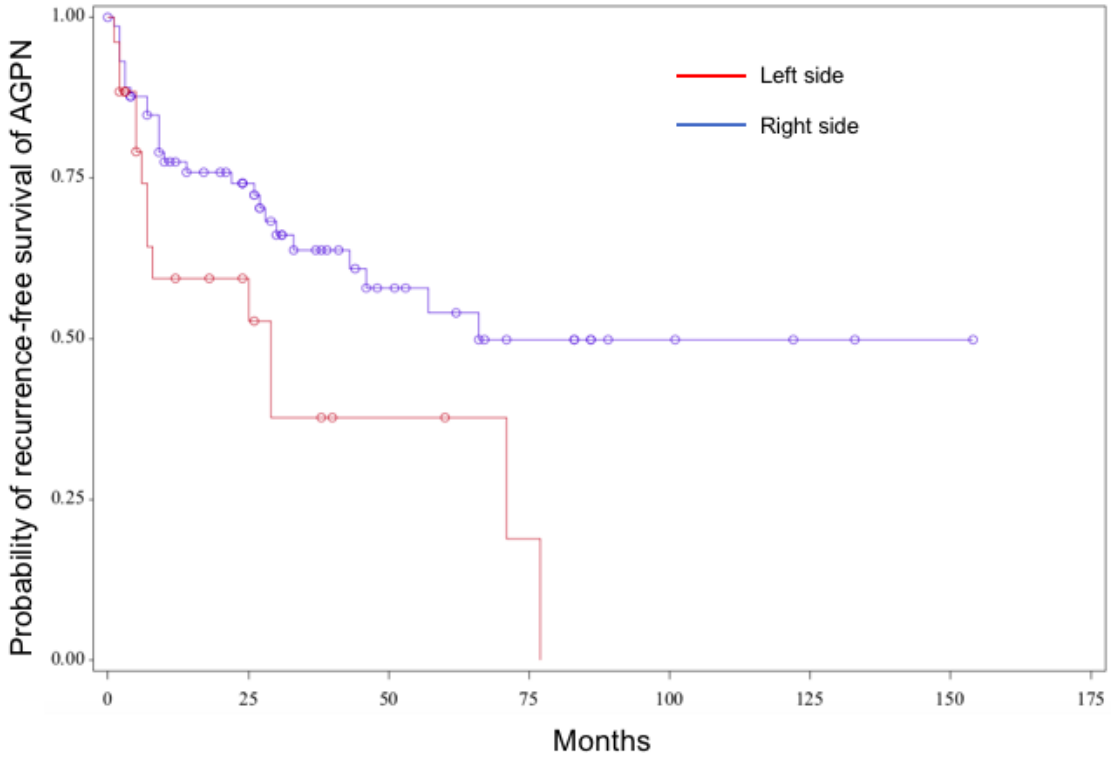



**Figure IV: Recurrence-free survival of AGPN after EPI according to the side of transplantation (*p*=0,022)**

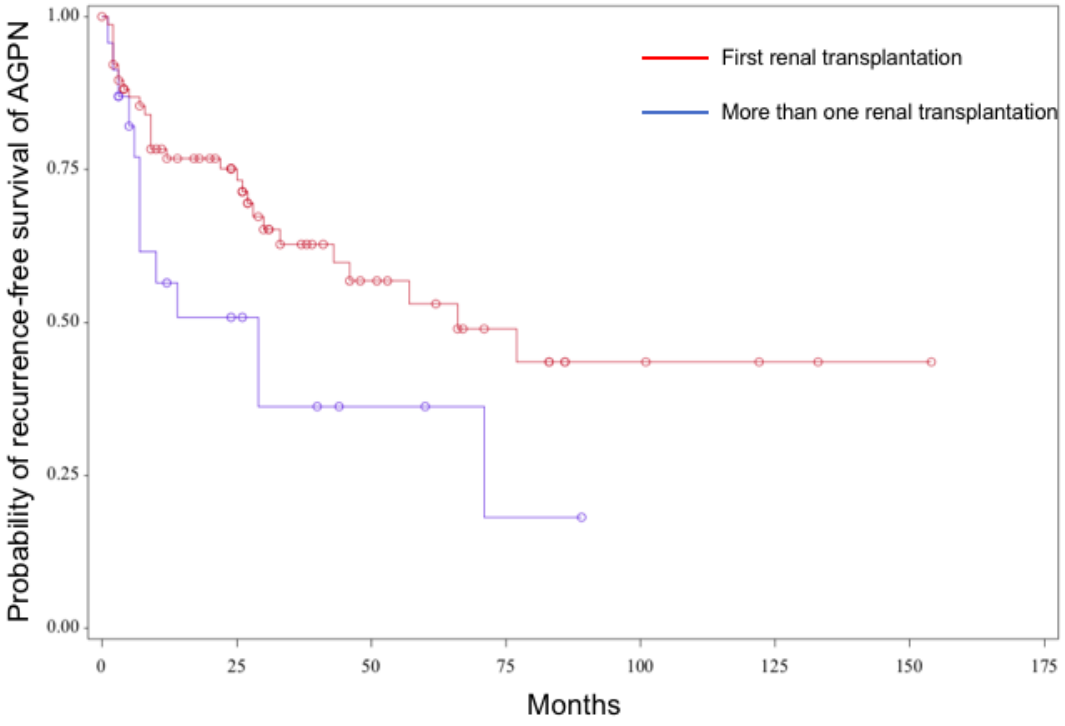



**Figure V: Recurrence-free survival of AGPN after EPI according to the rank of transplantation (*p*=0,045)**

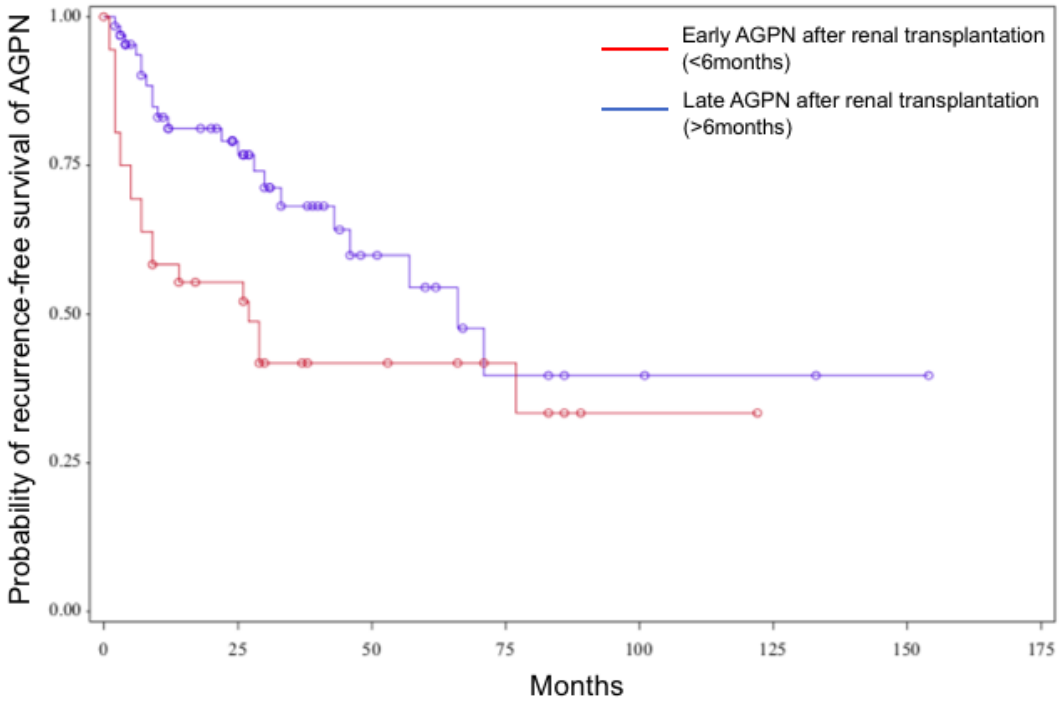



**Figure VI: Recurrence-free survival of AGPN after EPI according to delay between AGPN and the renal transplantation (*p*=0,028)**

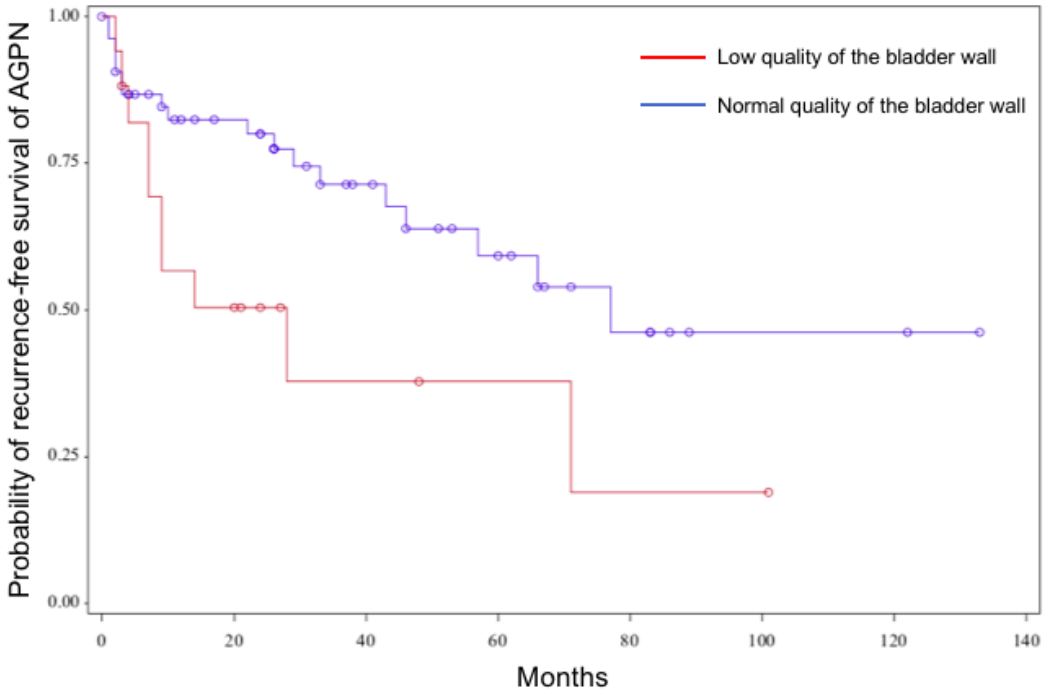



**Figure VII: Recurrence-free survival of AGPN after EPI according to the quality of bladder wall (*p*=0,036)**

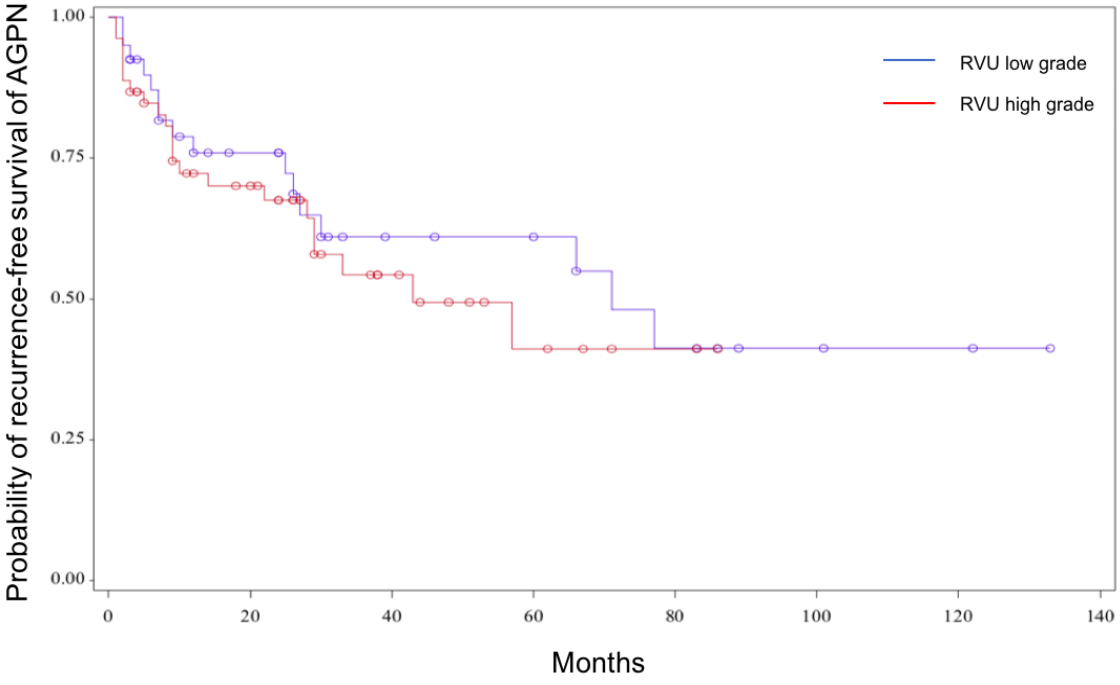



**Figure VIII: Recurrence-free survival of AGPN after EPI according to the grade of RVU (*p*=0,509)**

In multivariate analysis, residual diuresis (*HR* 2,4, (CI 1,2-4,5); *p*=0,010), early AGPN after transplantation (*HR* 2,1, (CI 1,1-3,9); *p*=0,020) and left side of transplantation (*HR* 2, (CI 1,0-3.9); *p*=0,047) were associated with the risk of EPI failure. The quality of bladder was not studied because of number of data missing (32 cases). In this cohort, the failure of EPI was respectively 25%, 76,5% and 100% in patient with one, two or three risk factors of failure (**Figure IX**).

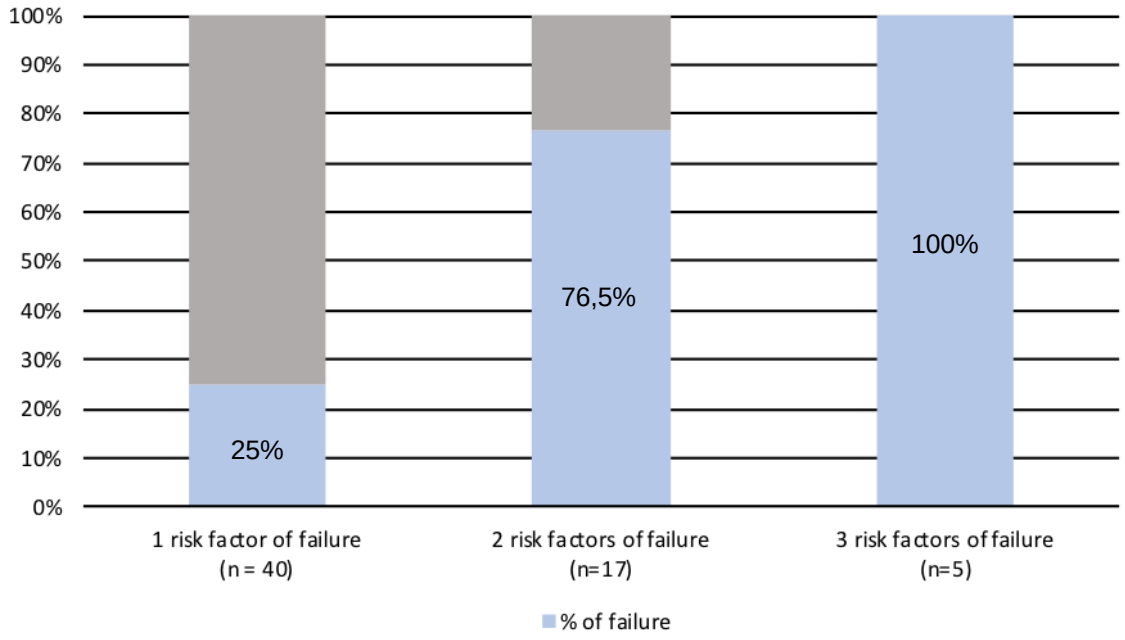



**Figure IX: Rate of failure of EPI according to the number of risk factor per patient**

## DISCUSSION

Symptomatic VUR has two types of management: either an open surgical re-implantation or an endoscopic management by bulking agents. Regarding the endoscopic management, Mallet et al, who had previously used polytetrafluoroethylene had 53,3% of success in their cohort of 15 patients(20), Aristizabal et al., reported using polydimethylsiloxane with a 70,6% success in 17 patients(21). Pichler et al., found 57,9% with dextranomer/hyaluronic acid copolymer in 19 patients(22) and Yucel et al., with the same agent found a similar result in 26 patients(53,8%)(23).

The largest cohort published presently was composed by 58 patients treated by dextranomer/hyaluronic acid copolymer or polydimethylsiloxane with 56,1% of success(24). Our results were similar but with the advantage of having a much larger cohort and a longer follow up data. We believe our results are slightly underestimated due to the fact that seven patients were considered to be clinical failure although they had a radiological success. In these cases, relapsing AGPN probably had another etiology. Moreover, five patients with a failure of procedure didn't have VCUG at the point of data collection, some of them could possibly also have a clinical failure and a radiological success. Thereby we estimate that success of the endoscopic procedure was probably closer to 2/3 of our cohort. The difficulty to define criteria of endoscopic treatment success or failure makes the results of each study hardly comparable, especially since different bulking agents are being used in different studies.

We can notice, our cohort was mainly composed by female (79,6%) who are more exposed to urinary tract infection due to the shortness of their urethra associated with immunosuppressive therapy.

Endoscopic treatment performed in native VUR in adult(16) or children(17) have better results than in VUR post transplantation. This can be explained by the scar and fibrosis secondary to vesicoureteral anastomosis(22), but also by the fact this anastomosis is mainly made on the lateral side of the bladder or on the dome. As a result this causes a non-orthotopic position of the ureteral orifice which has consequences; first, a difficult access with the rigid endoscope making the injection of bulking agent more complicated(22)(23)(25)(26), second, a vesico-ureteric junction with abnormal tissue compared to normal ureter locality, and third, a possible decreasing in the efficiency of bulking agent(26).

Despite the failure of the management, it's important to note that the number of AGPN significantly decreased after endoscopic treatment. This suggests there is an improvement of quality of life

and we should consider the failure of EPI as partial(21)(22). Moreover, after a failure of procedure, renal function remains similar, and second line of treatment, regardless of the type of management, appears perfectly achievable. Indeed, the presence of a bulking agent in bladder wall does not impede a second injection(22)(24) and a surgical re-implantation is not prevented since it is performed away from to the site of bulking agent.

Here we demonstrate the adverse effects of endoscopic treatment were 3,9%, similar to others studies(20)(21). Among these adverse effects, 2 patients had a temporary obstruction that can be explained by a tumescence and inflammatory process around the neo-orifice(22). Thus, adverse effects in endoscopic procedure do not cause serious damage when compared to those after a surgical re-implantation(27). Indeed, because of the transplantation, tissues are fibrotic and make this management more difficult(28) with a potential risk of severe side effects such as ureteral stenosis, urinary fistula, and ureteral necrosis. These side effects can lead in the worst case situation to graft loss(23). Due to the high impact of this surgery on the patient, and the potential morbidity, hospital observation time after surgical re-implantation is widely extended compared to endoscopic management which is achievable in outpatient surgery(1)(15).

Although EPI can be proposed as a first line of treatment, some risk factors of failures were identified. Among them, the absence of residual diuresis before the transplantation. The bladder is a muscle so if it doesn’t work it becomes atrophic and fibrosis can appear(29). The vesicoureteral anastomosis is technically harder due to tissue weakness(30). Thus, if the thickness of the bladder wall is involved in the success of the anti-reflux surgical re-implantation it should also be involved in polydimethylsiloxane efficiency.

The side of incision and the rank of transplantation were identified as risk factors for management failure and are associated because usually the second renal transplantation is made on the patient’s left side. Thus, a left incision, or a second renal transplantation, means patients have

already been operated. Moreover, patients who are candidates for a second renal transplant are often dialyzed, without residual diuresis. Therefore, the treatment is performed in a scarring bladder with the same consequences as previously described(29)(30).

The quality of bladder which was a subjective interpretation gave by the surgeon during transplantation is also a risk factor of endoscopic management failure. Indeed, a chronic empty bladder, retracted, with a very thin and weak wall will not provide sufficient support for the bulking agent, and this leads to a poor efficiency.

Finally, AGPN episodes less than 6 months after transplantation were also identified as a risk factor of failure. Since we observed endoscopic treatment have the same success in low or high grade VUR, we cannot interpret early infections as an indicator of high VUR. It is most likely correlated with other medical factors responsible for causing AGPN with which endoscopic management is ineffective.

A multivariate analysis confirmed the significance of some factors previously found. These include the absence of residual diuresis, the side of incision, and the presence of early AGPN after transplantation. The quality of the bladder was not assessed in the multivariate analysis due to a high number of missing data points. Regardless, we believe it would be a highly significant risk factor because the absence of residual diuresis and the side of incision are linked with the quality of bladder.

The presence or absence of these risk factors allows the prediction of the risk of failure for each patient. Thus, in our cohort, 76,5% and 100% of patients had a failure of treatment when they had respectively two or three risk factors of failures while patients with only one had 25% of failure. We believe that for a patient that has 3 risk factors of failure, an open surgery re-implantation should be achieved while in case of two risk factors, endoscopic treatment could be discussed.

There is a number of identifiable limitations to this study. First, this was a retrospective study with

several data missing and a risk of potential selection bias as it only sampled a single medical center. Second, the control voiding cystourethrography was almost only performed exclusively in patients with a failure of EPI. It could be interesting to also evaluate the patients with a clinical success since VUR is not always symptomatic.

## CONCLUSION

Effects of VUR associated to AGPN remains controversial on the graft survival and prevention is currently based on an open surgical re-implantation, which can have high perioperative morbidities. Nevertheless, the primary goal after a renal transplantation, must be to preserve the renal graft as long as possible. Thus, EPI appears to be a suitable management regardless the grade of the reflux. Even if EPI efficiency is lower than surgical re-implantation, it has advantages in being quick, secure, minimally-invasive, and low cost. Endoscopic management should be used in the first line of treatment to prevent recurrent AGPN secondary to VUR. However, open surgical re-implantation keeps a good indication if a patient has all risk factors for IEP failure.

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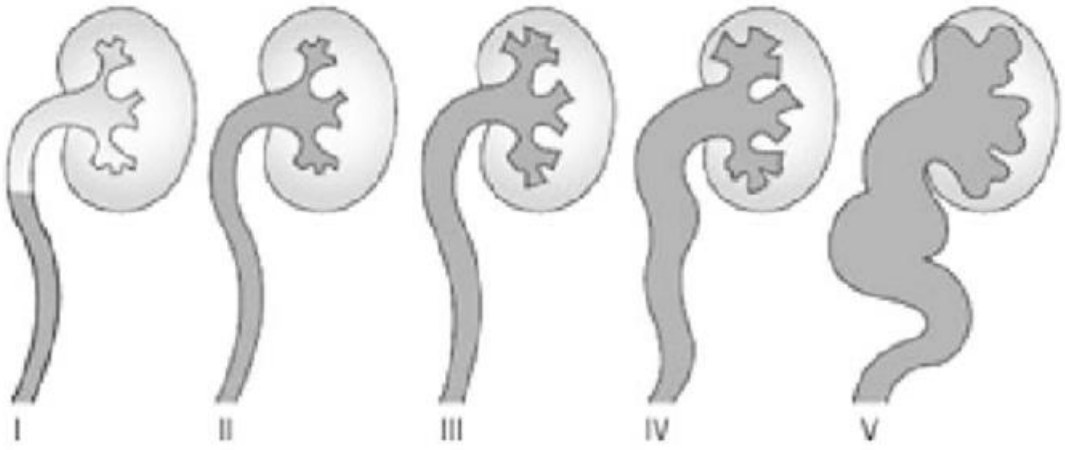
# CONCLUSION GÉNÉRALE

L'effet des pyélonéphrites aiguës du greffon secondaires à un reflux vésico-urétéral sur la survie du greffon reste controversé. Actuellement la prévention des récidives de PNAG repose sur une réimplantation chirurgicale ouverte qui est efficace mais au prix d'une morbidité élevée. Dans un contexte de pénurie d'organe associée à une augmentation de l'incidence de l'insuffisance rénale chronique, la sauvegarde du greffon apparaît donc comme une priorité absolue. La prévention des récidives des PNAG par injection endoscopique de polydimethylsiloxane semble être un traitement adapté. Bien que l'efficacité de cette prise en charge soit inférieure à celle de la réimplantation chirurgicale ouverte, elle a l'avantage d'être mini invasive, facile de réalisation, de faible morbidité et de coût réduit. La prévention de la récidive des PNAG post RVU par injection endoscopique de polydimethylsiloxane en première intention est donc justifiée néanmoins la réimplantation chirurgicale ouverte garde une bonne indication lorsque tous les facteurs d'échec du polydimethylsiloxane sont réunis.

# ANNEXE

**Annexe 1 :** Classification internationale des grades d'un reflux vésico-urétéral




| Grade | Description |
|---|---|
| I | Into a nondilated ureter |
| II | Into the pelvis and calyces without dilatation |
| III | Mild to moderate dilatation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices |
| IV | Moderate ureteral tortuosity and dilatation of the pelvis and calyces |
| V | Gross dilatation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity |

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Évaluation du traitement de première intention du reflux vésico-urétéral par injection endoscopique de polydimethylsiloxane chez 103 transplantés rénaux en prévention des récidives de pyélonéphrites aigues du greffon

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## Résumé :

**Introduction :**
Le reflux vésico-urétéral (RVU) sur transplant rénal peut favoriser les pyélonéphrites aigues du greffon (PNAG) et mettre en péril sa survie. La prise en charge chirurgicale de ce RVU par réimplantation chirurgicale ouverte est le gold standard mais est associée à une morbidité pouvant conduire également à la perte du greffon. L'objectif de cette étude était d'évaluer l'efficacité de l'injection endoscopique de polydimethylsiloxane (IEP) sur la prévention des récidives de PNAG associées à un RVU.

**Matériels et méthodes :**
Une étude monocentrique rétrospective a été conduite de janvier 2000 à décembre 2017. Tous les patients ayant eu une PNAG associée à un RVU et traités en première intention par IEP ont été inclus. Le RVU était diagnostiqué et classé en bas ou haut grade par urétrocystographie rétrograde et mictionnelle. L'efficacité de l'IEP était jugée sur la récidive ou non de PNAG.

**Résultats :**
103 patients ont été inclus sur 1811 transplantations rénales. 44% avaient un RVU de bas grade et 56% de haut grade. La prise en charge endoscopique était un succès dans 59,2% des cas avec un suivi médian de 43 mois. Il n'y avait pas de différence en fonction du grade du RVU. Les facteurs de risque d'échec de l'IEP en analyse multivariée étaient l'absence de diurèse résiduelle avant la greffe rénale (*HR* 2,4; *p*=0,001), la survenue de PNAG précocement après la transplantation (*HR* 2,1; *p*=0,020) et la greffe en fosse iliaque gauche (*HR* 2; *p*=0,047). L'échec de l'IEP était de 100% lorsque les patients présentaient ces 3 facteurs de risque. Parmi les patients ayant eu un échec d'IEP, un traitement de deuxième ligne par nouvelle IEP ou réimplantation chirurgicale ouverte a été efficace dans respectivement 80% et 81,2% des cas. Aucun effet secondaire grave n'a été constaté après cette prise en charge de première ligne.

**Conclusion :**
Le traitement du RVU par IEP est un traitement mini invasif, efficace, facile de réalisation, de faible morbidité et de coût réduit, justifiant son utilisation en première intention dans la prévention des récidives de PNAG. Toutefois la chirurgie classique par réimplantation chirurgicale ouverte paraît plus adaptée lorsque tous les facteurs de risque d'échec de l'IEP sont réunis.

## Composition du Jury :

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**Assesseurs :**
**Monsieur le Professeur Arnauld VILLERS**
**Monsieur le Professeur Philippe PUECH**
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