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THE CANDIDATE FOR RENAL TRANSPLANTATION WORK UP: MEDICAL, UROLOGICAL AND ONCOLOGICAL EVALUATION


Summary.- Renal transplantation prolongs life, reduces morbidity, improves quality of life, and enables social rehabilitation of patients with end stage renal disease (ESRD). Kidney transplantation is a surgical procedure with inherent risks due to anesthesia and the surgical procedure itself.

In ESRD patients medical background and comorbidities are crucial at the time of considering a renal transplant candidate because they can determine the procedure success.

OBJECTIVES: To update and review, according to recent literature, the evaluation of renal transplant candidates.

METHODS: We performed a retrospective review of medical literature published in Medline/Pubmed about the most important facts of medical, urological and oncological evaluation of ESRD patients candidates to renal transplant.

RESULTS: Pretransplant medical evaluation aims to diagnose, treat, and optimize any preexisting disease, and how these can interfere with patient and graft survival. It is important to consider age, cardiovascular disease, presence of diabetes mellitus, coagulation disorders, obesity, gastrointestinal diseases, ESRD situation and associated complications, active infection and non compliance with treatment and follow up.

Urological requirements for successful renal transplantation are the absence of urinary infections, a compliant and continent reservoir, and a reliable method of achieving complete bladder evacuation. Certain urological diseases may not be obvious in the anuric patient. Pretransplant urological evaluation aims to diagnose, treat, and optimize any preexisting urological disease that can jeopardize transplant evolution.

Cancer is a frequent and recognized complication of organ transplantation. The need of continuous immunosuppressive therapy may lead to immunosuppression-related side effects and direct oncogenic effects. Pre-existing malignancies should be extensively evaluated before proceeding to transplantation. Appropriate screening for malignancies is recommended in ESRD patients during routine pretransplant evaluation.

CONCLUSION: This review highlights the importance of performing a comprehensive medical, urological and oncological assessment before transplantation. We will go through these mayor aspects of the evaluation

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La patología neoplásica es una frecuente y reconocida complicación asociada al trasplante de órganos. El tratamiento inmunosupresor puede condicionar efectos secundarios directos así como un potencial efecto oncológico. Los tumores preexistentes deben evaluarse concienzudamente antes de realizar el trasplante, así como la existencia de una neoplasia oculta.

CONCLUSIÓN: En esta revisión destacamos la importancia de realizar una exhaustiva evaluación médica, urológica y oncológica antes del trasplante renal. Repasaremos los principales aspectos de la evaluación de los enfermos en IRCT, que pruebas diagnósticas se deben aplicar y cuáles son las últimas recomendaciones al respecto.

Es imprescindible una evaluación cuidadosa de cada candidato a entrar en lista de espera para trasplante para mejorar la supervivencia de injerto y receptor. El estudio debe ser individualizado según la condición particular de cada paciente, a través de un abordaje multidisciplinar antes de proceder con el trasplante.


INTRODUCTION

Renal transplantation is widely accepted as the most effective form or renal replacement, and prolongs patient survival, reduces morbidity, improves quality of life and facilitates social rehabilitation of patients with end stage renal disease (ESRD) (1). While the number of organs available for transplantation is limited, the number of patients with ESRD is increasing (2). Transplantation should be offered to all patients with advanced and irreversible renal failure, comprising stage IV disease with a glomerular filtration rate of under 30 ml/min/1.73 m2 (3, 4).

Patients with ESRD who are candidates for inclusion in the transplant waiting list are to be subjected to careful evaluation, due to inherent risks and potential complications of surgery, the postoperative period, and subsequent life as a kidney transplant recipient. ESRD population, particularly those who have spent most time of renal replacement therapy, have a high incidence of concomitant illnesses. During the pretransplantation evaluation, a thorough clinical history must be compiled, with special attention to those disorders that constitute a contraindication to transplantation, or which may have an impact after grafting (Table I) and to correct...
those clinical, surgical and psychological disorders that may affect the course of the patient (1, 2). Each case must be evaluated on an individualized basis, and the decision relating to treatment is to be taken in the context of a multidiscipline team (1).

The urinary tract of the candidate for renal grafting must be sterile and have an efficient reservoir. The bladder must be able to store a sufficient amount of urine at low pressure, with a competent sphincter system and safe mechanism for ensuring complete voiding via either spontaneous micturition or intermittent auto-catheterization (5-7).

Patients with ESRD have a higher cancer risk than the general population. Neoplastic diseases are the cause of death in up to 26% of all transplant patients that survive for at least 10 years (8). Malignancy is a well-recognized complication of transplantation; organ recipients in turn have a high incidence of tumors, reaching up to 40% after 20 years, versus only 6% among the non-transplanted population (9). Several hypotheses have been postulated: the ESRD itself, together with some drugs used for its treatment or some of renal malfunction consequences (dysfunction of immune system, nutritional deficiency, metabolic changes, accumulation of carcinogenic agents). Perhaps the interaction of all these facts with well-known carcinogenic agents, like tobacco, alcohol or ultraviolet radiations (5, 10). This risk is even greater in ESRD patient who receive a renal transplantation (11). Three factors account for this increased cancer incidence on this population group: immunosuppressive treatment, oncoviruses and a theoretical oncogenic effect of the immune suppressor drugs administered (12).

The objective of this review is to analyze aspects of medical, urogenital and oncological evaluation of the ESRD patient prior to a renal transplantation. The urologist must focus the attention on these pathologies during the pretransplant evaluation.

MATERIAL AND METHODS

Between September 2009 and January 2010, we performed a retrospective review of recent medical literature (from 2005 to 2009) in Medline/Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) about the most important issues to check during pretransplant evaluation of renal transplant candidates. We used key words “chronic kidney failure”, “kidney transplantation”, “medical workup”, “candidates”, “pregnancy”, “urinary tract” and “neoplasm” obtaining 3905 references, of which we select relevant and review articles about the proposed subjects. Papers reviewed from before 2005 are of special interest about the proposed subject.

Despite the limited, usually papers from non-well designed studies, and contradictory literature we try to summarize the most important points, adapt their application to current daily clinical practice, actualize and simply the study of ESRD patients candidate to transplantation.

RESULTS

A. Medical evaluation and medical records:

a) Age: Age is not a barrier for renal transplantation, however access to the transplantation program should be limited to those patients with a life expectancy that can ensure prolonged graft survival (1, 4).

In pediatric patients early grafting is indicated to reduce the time on dialysis and minimize the impact of ESRD upon growth, development and nutritional status (13, 14). Regarding potential

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**TABLE I. CONTRAINDICATIONS TO KIDNEY TRANSPLANTATION (23).**

<table>
<thead>
<tr>
<th>CONTRAINDICATIONS TO KIDNEY TRANSPLANTATION</th>
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<tbody>
<tr>
<td>Reversible kidney disease</td>
</tr>
<tr>
<td>Active neoplasm</td>
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<tr>
<td>Active acute or chronic infection</td>
</tr>
<tr>
<td>Glomerulonephritis or active vasculitis</td>
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<tr>
<td>Severe lung or cardiovascular disease</td>
</tr>
<tr>
<td>Severe chronic liver disease</td>
</tr>
<tr>
<td>Life expectancy of less than one year</td>
</tr>
<tr>
<td>Patient non-compliance</td>
</tr>
<tr>
<td>Active substances abuse</td>
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<tr>
<td>Uncontrolled psychiatric disorders</td>
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recipients over 60 years of age, the necessary considerations before inclusion on the waiting list are related to the presence of disorders that can adversely affect the course (cardiovascular disease, osteodystrophy or occult neoplastic processes or signs of cognitive impairment) (1, 15, 16). Transplantation has revealed lesser global mortality in patients over age 65 years than among those on the waiting list (17), though postponing surgery in patients of this kind significantly lessens the benefits obtained (18). In this age group postoperative complications rate is very high, particularly when the organ comes from an elderly donors (19). These subjects have increased infection frequency, severity and mortality, together with a greater risk of developing concomitant illnesses or neoplasms (16, 20-22).

b) Cardiovascular disease: cardiovascular illnesses are the main cause of death after transplantation (includes ischemic heart disease, peripheral vascular disease and cerebrovascular disease) (23-26). Patients with ESRD have a high prevalence of ischemic heart disease, left ventricle hypertrophy and congestive heart failure, and are therefore at a high risk of developing perioperative and post-transplantation complications (3). All cardiovascular risk factors are to be identified during the pretransplantation evaluation process (Table II).

Immunosuppressive therapy, particularly corticoids and anticalcineurinic agents, worsens the cardiovascular risk factors in a dose-dependent manner (hypertension, hyperlipidemia, hyperglycemia) (27). It is well known that smoking is a risk factor for cancer and cardiovascular diseases in the general population, and it is therefore logical to assume that these complications also increase in the transplant population (28). Observational studies have shown that smoking increases the risk of cardiovascular events and reduces patient and graft survival (29-31).

1) Ischemic heart disease: the existence and severity of coronary disease plays a key role in determining whether a given patient is a candidate for kidney transplantation or not. ESRD patients with cardiovascular disease present longer survival after transplantation than if they remain on dialysis (32), though perioperative morbidity is greater (33). The risk factors (Table II), along with the patient age and causes underlying ESRD, must alert us to the possible presence of silent ischemic heart disease (4). In risk subjects, and in addition to the clinical history and basic study (ECG and plain chest X-rays), a series of procedures are indicated depending on the type of suspected pathology:

- **Echocardiogram**: this is performed to evaluate valve disease, cardiomyopathy, or systolic/diastolic left ventricle dysfunction (34).
- **Exercise testing**: this is performed to discard possible ischemic heart disease. In case of limited patient mobility, this technique is to be substituted by thallium perfusion scintigraphy (35) or dobutamine echocardiography (26).
- **Coronariography**: This is indicated in cases strongly suggestive of ischemic heart disease (36).

In the event coronary revascularization proves necessary (surgical or via angioplasty with stent placement), it must be carried out before transplantation (1). When a patient presents coronary disease not amenable to revascularization, transplantation is generally considered contraindicated (4).

2) Peripheral vascular disease: potential transplant candidates are to be carefully evaluated in relation to signs or symptoms of this disease, since it is common in ESRD patients (37). Peripheral vascular disease may be a contraindication to heterotopic transplantation, lead to technical failure of surgery, and even generate a risk of amputation of the homolateral lower extremity (1).

On a routine basis, and in addition to physical examination with pulse assessment and an evaluation of possible arterial murmurs, a plain abdominal X-ray study is indicated (38). If the patient presents risk factors (Table II), vascular calcifications, or signs or symptoms of arterial occlusion, an echo-Doppler study of the peripheral arteries (39) and/or signs or symptoms of arterial occlusion, an echo-Doppler study of the peripheral arteries (39) and/or a thoracoabdominal CT scan without contrast administration is required (1). In patients with severe peripheral vascular disease, angiography should be considered, with the assessment of pretransplantation vascular repair (1).

3) Cerebrovascular disease: such pathology can be an important source of postoperative morbidity-mortality. When signs or symptoms, risk factors (Table II) or vascular calcifications are observed, the study is to be completed with an echo-Doppler exploration of the supraaortic trunks (1).

Patients with polycystic kidney and hepatic disease (PKHD) must undergo cranial CT if there is a familial history of intracranial aneurysms (4).

Epileptic patients subjected to treatment are to be referred to the neurologist for evaluation, since some antiseizure drugs interfere with the metabolism of anticalcineurinic agents. Suspension is required of those drugs that are not essential, or a treatment...
regimen involving a lesser interaction potential should be adopted (3).

c) Diabetes mellitus: diabetes mellitus (DM) is not a contraindication to transplantation (40). The diabetic patient must be aware that post-transplantation blood glucose control commonly worsens as a result of renal recovery of insulin metabolism and the use of immunosuppressor drugs (which can alter insulin production or sensitivity) (4).

Renal transplantation or combined kidney-pancreas transplantation reduces morbidity and mortality over the long term with respect to dialysis in patients with ESRD (41). These patients have a higher mortality and poorer graft survival compared with non-diabetic patients (17). In patients with insulin-dependent DM and ESRD, kidney-pancreas transplantation is the best option for the combined management of both diseases (3, 4, 42).

Due to the high prevalence of cardiovascular disease in this group of patients (4, 33), an exhaustive study is required to discard silent cardiovascular pathology. Neurogenic bladder is a frequent complication in diabetic patients, and as such requires special attention (43).

d) Coagulation disorders: patients receiving anticoagulation or antiplatelet treatment are not to be excluded from the transplant waiting list. In both cases, appropriate measures are to be introduced at the time before grafting, with special caution during surgery to avoid postoperative bleeding (1).

Coagulation disorders have a negative impact upon graft survival due to increased risk of post-transplantation thrombosis (44). Renal graft thrombosis is recorded in between 1-5% of all transplant cases, and this risk is much higher among graft recipients with antiphospholipid antibodies, nephrotic syndrome, or when the graft arteries are of small size (14, 23). Patients with ESRD paradoxically have an increased bleeding risk secondary to uremic platelet dysfunction and the anticoagulation medication administered during dialysis (45). Following kidney transplantation, special attention should focus on checking hemostasis of the surgical bed.

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**TABLE II. RISK FACTORS FOR CARDIOVASCULAR DISEASE (1, 3, 4, 25, 26).**

<table>
<thead>
<tr>
<th>RISK FACTORS FOR CARDIOVASCULAR DISEASE</th>
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<tbody>
<tr>
<td>Arterial hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes mellitus for over 25 years</td>
</tr>
<tr>
<td>Diabetic nephropathy in patients under age 45 years</td>
</tr>
<tr>
<td>ESRD and prolonged renal replacement therapy</td>
</tr>
<tr>
<td>Elderly subjects</td>
</tr>
<tr>
<td>History of ischemic heart disease (personal or in relatives at a young age)</td>
</tr>
<tr>
<td>Chronic corticoid therapy</td>
</tr>
<tr>
<td>Severe peripheral vascular disease</td>
</tr>
<tr>
<td>Severe cerebrovascular disease or history of stroke</td>
</tr>
<tr>
<td>EKG alterations (left ventricle hypertrophy, Q-waves, ST-segment alterations, bundle block, arrhythmias)</td>
</tr>
</tbody>
</table>
Hypercoagulability rarely constitutes a contraindication to transplantation, though it does require the introduction of anticoagulation or antiplatelet therapy on an early basis, which while increasing the risk of bleeding is also able to prevent graft thrombosis (3, 4, 46). As part of the pretransplantation workup, an evaluation of coagulation disorders is required, particularly in patients with a history of recurrent miscarriage, thrombosis of the dialysis arteriovenous fistula, systemic lupus erythematosus, previous loss of a graft due to unjustified thrombosis, or other thrombotic events (3, 4). In addition to a basic coagulation study, the pretransplantation laboratory tests of this risk group must include ATIII, C-reactive protein, Leiden factor V, S protein, homocysteine and antiphospholipid antibodies (1, 4, 23).

e) Obesity: overweight patients show a high complications rate associated to transplantation (47). Obesity is correlated to an increased risk of cardiovascular disease, graft dysfunction and loss, a prolongation of hospital stay, and the development of post-transplantation DM (3, 48, 49). However, although these are high-risk patients, grafting improves survival and quality of life in obese individuals with ESRD (4, 50).

The existing body of evidence is insufficient to exclude from the waiting list those patients who exceed a given body mass index (BMI) – though most centers use a cutoff value corresponding to BMI > 40 kg/m2 (3, 4). In these patients the evaluation made by the surgical team in charge of transplantation is an essential consideration, since body configuration can condition surgical success (4).

A careful pretransplantation assessment is required, together with insistence on the need to lose body weight before surgery, in order to reach BMI < 30-35 kg/m2 (1, 4, 48). Patients with background cardiovascular disease are not to undergo transplantation until effective weight loss has been achieved (48). A recent study has shown that obese patients suffer an increased number of complications when weight is gained during the postoperative period; accordingly, the weight loss prior to surgery must be maintained after transplantation (51).

f) Diverticulosis with / without diverticulitis: an intraabdominal infection or perforated hollow organ may prove disastrous for immune suppressed patients. When the patient presents a history of diverticulitis, especially if it is recurrent, the need for a segmental sigmoidectomy prior to transplantation must be considered (4, 52). It does not seem advisable to screen all transplant candidates for diverticuli, except in those with PKHD (4).

g) Cholelithiasis and choledocholithiasis: the presence of cholelithiasis detected by pretransplantation abdominal ultrasound may be an indication for cholecystectomy. In immune suppressed individuals, particularly in the presence of diabetes, cholecystitis generates important morbidity-mortality (4, 23).

h) Cirrhosis: the principal cause of liver cirrhosis in candidates for kidney transplantation is viral hepatitis (4). Cirrhosis is a contraindication to kidney transplantation, due to the high mortality observed in this group – though in selected cases dual liver and kidney transplantation can be contemplated (3).

All patients with HBV antigens and/or antibodies against HCV must undergo testing to assess viral load (53). Transaminase determination offers low sensitivity in detecting the degree of liver damage (23); as a result, liver ultrasound is to be requested in patients with positive viremia, together with the determination of alpha-fetoprotein (AFP), and the patient should be referred to a specialist in gastroenterology for evaluation and possible liver biopsy (53). In patients with HCV viremia without cirrhosis, antiviral therapy may be offered to suppress viral replication before transplantation (3, 4). The option of transplantation from an HCV-positive donor should be examined with the patient; since the waiting list is consequently shorter, and acceptable results are obtained (3). Patients with negative HBV serology are to be vaccinated against hepatitis B (3).

i) Hyperparathyroidism: in those cases where clinical management has been unsuccessful, or in patients with severe complications secondary to hyperparathyroidism, the possibility of parathyroid gland removal should be considered (54).

j) Situation of the ESRD: the longer a patient has been on dialysis, the greater the probability of concomitant disorders and important physical deterioration that can complicate the outcome of transplantation. All patients should be informed that transplantation can involve a dead or live donor, and that both options have their advantages and inconveniences. The timing of transplantation conditions percentage success and graft survival; accordingly transplantation should take place as early as possible, even before the patient requires
renal replacement therapy (55). Early transplantation occurs in 25% of all live donor operations and in fewer than 10% of the dead donor interventions (56).

Most patients with ESRD reach dialysis without knowing the cause of their renal failure (4). If the underlying cause is a systemic disorder, the latter must be treated and in remission before entering the transplantation waiting list (systemic lupus erythematosus, vasculitis, hemolytic-uremic syndrome, etc.) (40). The patient must be made aware of the risk of relapse, which the background illness implies for the graft (Table III) (23). Recurrence of the disease is the third most frequent cause of graft loss, after chronic rejection and patient death with a functioning graft (26). The risk of graft loss is similar in live and dead donor transplants. If there has been rapid graft failure due to the recurrence of glomerulonephritis, the risk of failure of the new graft is high (up to 80%). In these cases a second live donor graft should be avoided (3). Fortunately, many of such relapses are only observable at histological level and have no clinical repercussions -relapse being associated with a graft loss rate after 10 years of less than 10% (57).

Some diseases characterized by a high recurrence rate and early graft loss are considered to be contraindications to transplantation: anti-glomerular basal membrane antibodies, primary oxalosis and light chain storage disease (1). In the case of these patients inclusion on the waiting list could be considered after prior specific treatment (40), e.g., elimination of the antibodies targeted to the glomerular basal membrane, or assessment of combined liver and kidney transplantation. There are no recommendations in the clinical guides for ESRD patients with light chain storage disease, though management in the form of chemotherapy or bone marrow transplantation could be considered in such cases (1).

### Table III. ESRD Causal Disease. Percentage Recurrence of Disease in the Graft After Transplantation. Percentage Graft Loss Due to Recurrence of the Original Disease (26).

<table>
<thead>
<tr>
<th>Disease</th>
<th>% Recurrence Risk</th>
<th>% Graft Loss Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>50 (5 years)</td>
<td>5-35</td>
</tr>
<tr>
<td></td>
<td>100 (20 years)</td>
<td></td>
</tr>
<tr>
<td>Focal glomerulosclerosis</td>
<td>10-50</td>
<td>25-50</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>20-30</td>
<td>10-50</td>
</tr>
<tr>
<td>Membrane-proliferative glomerulonephritis I</td>
<td>20-50</td>
<td>5-30</td>
</tr>
<tr>
<td>Membrane-proliferative glomerulonephritis II</td>
<td>80-100</td>
<td>10-20</td>
</tr>
<tr>
<td>Anti-glomerular basal membrane disease</td>
<td>&lt;10</td>
<td>1</td>
</tr>
<tr>
<td>ANCA+ vasculitis</td>
<td>10-50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Lupus nephropathy</td>
<td>&lt;10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Schönlein-Henoch purpura</td>
<td>15-50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome (non-epidemic)</td>
<td>10-50</td>
<td>3-50</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>50</td>
<td>Frequent</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>&lt;20</td>
<td>Rara</td>
</tr>
<tr>
<td>Primary and secondary amyloidosis</td>
<td>10-40</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>50-70</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>100</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type I hyperoxaluria</td>
<td>90-100</td>
<td>Very frequent</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>No</td>
<td>No</td>
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</table>
Patients opting for second or successive transplantation, it is important to know the location of the previous graft, the reason for graft loss, the complications that developed, and patient compliance with the prescribed immunosuppressive regimen (3). In this group already exposed to immune suppression, special attention must focus on the exclusion of neoplastic disease, cardiovascular disease and possible immunological sensitization (40). After graft failure, the immunosuppressive dose should be gradually reduced and finally suspended, since the continuation of such treatment implies an increased complications rate (58). If the graft begins to produce symptoms (uncontrollable rejection, severe hematuria, tumor in the graft), graft removal (3, 59) or alternatively percutaneous graft embolization is indicated (60).

It is important to document the type of renal replacement therapy in the pretransplantation workup. In patients subjected to peritoneal dialysis, the presence of the dialysis catheter does not contraindicate surgery, though infection of the catheter is a contraindication (4). The patient must have remained at least two weeks free of symptoms after completing the cycle of antibiotic treatment, before transplantation is carried out.

**k) Treatment compliance:** despite the benefits of kidney transplantation, the latter is an elective form of treatment, and due evaluation is therefore required of patient motivation and commitment to the prescribed therapy and medical controls. The patient also must be evaluated for adequate social and family support (4, 61). In addition, it is essential to discard alcohol and drug abuse, and to recommend smoking cessation.

A lack of compliance or adherence to immunosuppressive therapy is considered an important cause of late graft dysfunction and graft loss (61). The proportion of adults that fail to comply with treatment or with follow-up after transplantation reaches 22.4% (62) – this percentage is even higher among adolescent patients (61).

Education programs are essential for reducing the percentage of patients who fail to comply with follow-up, and for improving patient implication. Such programs explain the function, importance and side effects of the different drugs, and seek to implicate the patient in his or her personal treatment (61).

**l) Pretransplant and infection:** infections are an important cause of morbidity and mortality in transplant patients, particularly when these are receiving intensive immune suppressive therapy (1). As part of the pretransplantation workup, evaluation is required of all active infectious process that could place the immediate future of the graft at risk (54). In contrast, chronic infections pose no immediate post-transplantation risk (1). When chronic infection is identified, treatment may be administered before transplantation, or prophylaxis can be provided to avoid reactivation after grafting (4).

Screening is indicated for HBV, HCV, HIV, tuberculosis, CMV, Treponema pallidum, EBV, HTLV, HSV and VZV (4, 20, 54, 63). Regarding HBV and HCV, see previous diseases (see previous in this medical evaluation h. Cirrhosis). At present, between 2.5% of all ESRD patients are HIV-positive, and most of these individuals are under 50 years of age (23). HIV screening is recommended, since active infection is a contraindication to transplantation (32). Retrospective studies have shown that successful transplantation is possible in HIV-positive patients receiving antiretroviral therapy who have not developed AIDS, with an undetectable viral load, and with a CD4+ cell count of over 200 cells/ml (3, 54, 64). In seropositive patients receiving antiretroviral therapy, special attention must center on the plasma concentration of the immunosuppressors, in view of the potential for interaction between the two drug groups (64). The recommended screening for tuberculosis (TBC) includes a detailed clinical history and a chest X-ray study (54). When positive, prophylactic measures are to be adopted to prevent TBC reactivation with immunosuppressive therapy after transplantation (1). In patients with a history of pulmonary tuberculosis, mycobacterial evaluation in urine is indicated. Other authors also recommend tuberculin (Mantoux) testing – positivity being accepted for an induration of ≥ 10 mm (in which case a 9-month cycle of isoniazid should be administered) (4). A positive Mantoux test does not contraindicate transplantation while treatment with isoniazid is completed. The serological status relating to cytomegalovirus (CMV) must be investigated in all patients, due to the high rate of serious infections due to this virus associated to immunosuppressive treatment (65). Due to its low prevalence, screening for syphilis is not considered obligatory, except in risk groups (1). Screening for Epstein-Barr virus (EBV) in turn is indicated in children and young adults, due to the risk of developing a lymphoproliferative disorder associated to EBV infection (63). In turn, human T lymphotropic virus (HTLV) has been implicated in adult T cell leukemia/lymphoma. Positive serology for this virus is not a contraindication to transplantation, though the patient should be referred to hematology for evaluation of the potential risk (4).

Special attention should be paid, with patients originating from endemic areas or those traveling to
them shortly before receiving transplantation to detect rare infectious diseases in our environment, such as Chagas disease, hemintiasis, parasitosis, malaria, etc...

m) Kidney transplantation and pregnancy: in recent years thousands of cases of pregnancy in transplanted patients have been reported (66, 67). ESRD patients often suffer sexual dysfunction and infertility, which can be reverted after transplantation (1, 68, 69). Patients should be advised to plan pregnancy for when they are in good general condition and the graft functions correctly (with normal ultrasound findings, no proteinuria, hypertension or signs of rejection) (68, 69). In the past, the recommendation was to avoid pregnancy before the second year after transplantation, though more recent studies have found that a shorter interval between grafting and pregnancy does not imply a risk for the mother or for the graft (70, 71). It should therefore recommend the use of any contraceptive method as a means of birth control on an individual basis, according to the wishes of each patient, resulting barrier methods, low dose estrogen-progesterone contraceptives or surgery (tubal ligation or vasectomy) the most suitable.

Pregnancy in a transplant patient usually progresses without problems, though such cases should be regarded as high-risk situations, and should be managed from a multidisciplinary perspective (obstetrics, nephrology and urology) (69). Special attention should center on the control of proteinuria, hypertension (preeclampsia affects 30% of the patients), kidney function and rejection, as well as the presence of bacteruria, symptomatic or asymptomatic, based on monthly urine cultures (69).

No differences have been found in the course of pregnancy or the graft with different immunosuppressive regimens (cyclosporine, tacrolimus, steroids, azathioprine) (71). Sirolimus is contraindicated during pregnancy, and mycophenolate should not be used, since there is increasing evidence that it has teratogenic effects (69, 72, 73).

The incidence of miscarriages and congenital malformations is similar to that recorded in the general population (1). Grafting in the iliac position poses no problems for vaginal delivery, though the high incidence of premature births and low weight at delivery cause the number of cesarean sections to increase (up to 50%) (67). Breastfeeding is not advised, since the infant could be exposed to immunosuppressive drugs excreted in breast milk (69). Vaccination of the newborn infant should be postponed until the age of 6 months (1).

B. Urologic evaluation:

Most authors agree about the importance of rule out the presence of abnormalities in the urinary apparatus in the renal transplant candidate (74). In general, urinary tract alterations are observed in up to 25% of all ESRD patients (75). Approximately 20-25% of all pediatric patients and 5-7.6% of all adults have ESRD of urological origin (5, 76). Congenital or acquired anomalies of the urinary system that have given rise to the existing ESRD must be corrected before considering the patient to be suitable for kidney transplantation (40, 77). Such correction must be carried out at least three months before the operation (except as refers to urethral pathology) (78).

The basic urological study comprises a detailed clinical history and physical examination (Table 6), complemented with urine sediment and abdominal ultrasound (5). Special attention must center on the existence of recurrent urinary infections or infravesical obstruction, micturition dynamics and the presence of residual diuresis. There are not formal recommendations, but perhaps for patients with residual diuresis, an urofluxometry with an estimation of residual bladder postvoiding volume is a valid and non-invasive test to evaluate inferior urinary tract function (7). Depending on the individual situation of each patient, and when certain disorders are suspected, additional complementary tests may prove necessary:

a) Bladder dysfunction: In general, performing a transplant on a patient with abnormal inferior urinary tract will need a close follow up after the implant (7). The existence of bladder dysfunction adversely affects renal graft survival and function (79).

It is not uncommon to find patients on dialysis with oliguria or anuria, and thus with a defunctionalized bladder. Urinary tract infections in the posttransplant period are more frequent in patients with long term non functioning bladder, despite the fact that it has not been observed more urologic complications due to a thickened and retracted bladder (80). In this patient group it is advisable to perform bladder irrigation with physiological saline through weekly auto-catheterization sessions, in order to avoid the development of a pyocyst prior to transplantation and rehabilitate bladder function and capacity (5, 81). Urinary tract infections are a serious problem after transplantation. For those patients with a normal bladder they do not jeopardize graft survival, meanwhile for those with a malfunctioning organ are more severe and represent a serious risk for the transplanted kidney (7). Due to this reason it is
recommended in this group of patients, to administrate antibiotic prophylaxis during the first 6 months after transplantation.

Serial micturition cystography (SMC) will help us to estimate bladder capacity, the presence of vesicoureteral reflux and determine the postmicturition residue (74, 82). Urodynamic study is indicated in all patients with anatomical abnormalities of the inferior urinary tract or symptoms of voiding difficulties and/or low bladder capacity (82, 83). In pediatric patients, a neurogenic bladder is the cause of up to 40% of all cases of ESRD. In these patients SMC is indicated when minimally suspecting bladder dysfunction, urinary tract malformations or recurrent infections, or on visualizing dilatation of the renal pelvis via ultrasound (84, 85). In adult patients, and unless there is a confirmed history or suspicion of bladder disorders, invasive studies are not made (SMC, urodynamic testing, urethrocystoscopy) (83).

Special attention should focus on the exclusion of a hypocontractile bladder, particularly in long-standing diabetic patients with peripheral neuropathy. We have limited options managing a high postmicturition residue due to a hypocontractile bladder, and these are voiding reeducation, micturition with abdominal press and clean intermittent catheterism.

A high bladder pressure (> 40 cm H2O) has been associated with damage to both, the native kidneys and the renal graft (82). There has been a worse graft outcome in relation to abnormal bladder pressure during voiding and high postmicturition residue, but has not shown this relationship with bladder capacity, maximum filling pressure or peak flow during voiding (7). Options to a high-pressure bladder including first, treatment with anticholinergics, which reduce the bladder pressure at the expense of increased postmicturition residue, so it may be necessary to associate intermittent catheterization (82). When the patient does not tolerate intermittent catheterization, or this maneuver is unsuccessful, should consider making a Mitrofanoff stoma (82). If action is not enough, you can choose from a bladder augmentation (which may require self-catheterization later) or a urinary diversion with bowel, at least 10-12 weeks before or after transplantation (5, 86).

Vesicoureteral reflux (VUR), associated with urinary tract infections or pyelonephritis, should be corrected before transplantation by ureteroneocystostomy or endoscopic injection of dextran copolymer hyaluronic acid (Deflux È, Oceana Therapeutics Inc, USA) (82). An uncorrected high-grade VUR significant increases morbidity to the graft (87).

### TABLE IV. PRETRANSPLANTATION LABORATORY TESTS.

*See on text; urological and oncological evaluation.

<table>
<thead>
<tr>
<th>PRETRANSPLANTATION LABORATORY TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete blood count and leukocyte formula</strong></td>
</tr>
<tr>
<td><strong>Erythrocyte sedimentation rate (ESR)</strong></td>
</tr>
<tr>
<td>Complete biochemistry</td>
</tr>
<tr>
<td>Blood group</td>
</tr>
<tr>
<td><strong>HLA</strong></td>
</tr>
<tr>
<td><strong>Serology</strong></td>
</tr>
<tr>
<td>HBV, HCV, HIV, CMV (IgM / IgG), VZV, RPR, HTLV, EBV</td>
</tr>
<tr>
<td>Mantoux test</td>
</tr>
<tr>
<td>Transplant candidate vaccination is to be checked for: HAV, HBV, pneumococcus, diphtheria, tetanus, pertussis, polio, varicella, measles, mumps, rubella</td>
</tr>
<tr>
<td><strong>Urine sediment and culture</strong></td>
</tr>
<tr>
<td>If the patient presents residual diuresis</td>
</tr>
<tr>
<td><strong>Mycobacteria in urine</strong></td>
</tr>
<tr>
<td>In the presence of a history of tuberculosis</td>
</tr>
</tbody>
</table>
A cystoscopy must be performed in patients with inconclusive SMC or suspected pathology requiring surgical correction pretransplantation (74). If we fail to restore an acceptable bladder function before transplantation, or due to a low capacity and compliance bladder that does not respond to the proposed treatment, should be evaluated for bladder augmentation surgery (14, 82). You can also perform transplantation with good results, to patients without lower urinary tract or major bladder disturbances, performing urinary diversion to an ileal conduit or continent reservoir or through a cutaneous ureterostomy (7).

b) Urethral alterations:

1) Posterior urethral valves: cause ESRD in up to 8% of the pediatric patient population (79). Treatment of this condition is required before transplantation, with special attention to bladder function. Early diagnosis and appropriate management of voiding dysfunction with intermittent catheterization and anticholinergic medication helps ensure graft survival comparable to transplanted population with a normal bladder (81, 88). The study of lower urinary tract must be determined by SMC and urodynamic study (81).

2) Urethral stenosis: when such alterations are suspected, flowmetry and postmicturition residue measurements are useful and noninvasive tools to assess initially this illness. These tests can be combined with urethrocytostopy and/or with a retrograde and perimciturition urethrography (5). In oliguric or anuric patients, treatment should be delayed (i.e., dilatation, internal urethrotomy, urethroplasty) until diuresis is achieved following transplantation, allowing the avoidance of restenosis “dry urethral syndrome” (89).

c) Prostate hyperplasia: all males over 50 years of age (or over age 45 years in the presence of a familial history of prostate cancer) are to undergo a rectal digital exploration, together with the determination of prostate-specific antigen (PSA) (1, 5, 90).

Flowmetry combined with ultrasound measurement of the postmicturition residue is an excellent screening option in asymptomatic patients with lower urinary tract obstruction.

The first line of treatment is clinical, in the same way as in the general population (administering alpha-blockers, 5-alpha-reductase inhibitors). If such measures fail, transurethreal resection of the prostate (TURP) should be considered. In an oligoanuric patient may end up generating urethral stenosis at the level of the prostatic space, this procedure therefore should be performed after transplantation (5, 91).

d) Pathology of native kidneys: see the indications for native kidney nephrectomy (Table VII). Bilateral nephrectomy implies important morbidity, strict fluid restriction, anemia (this problem is currently minimized thanks to the use of recombinant erythropoietin) and renal osteodystrophy (92). Depending on the indications, nephrectomy can be performed via open surgery (anterior or lumbotomy approach) or laparoscopically (1, 5, 82, 93). Surgery can be performed some time before or in the same act of transplantation (82).

e) Miscellaneous urological disorders: other pathologies can be identified in the course of the pretransplantation workup, such as hydrocele, chronic epididymitis, scrotal herniation or hypospadias. If treatment proves necessary in such situations, it should be completed before transplantation (5).

C. Oncological evaluation:

Any active tumor is regarded as an absolute contraindication to transplantation (1). The evolution of the disease in transplanted patients tends to be more aggressive and offers less survival in comparison with general population (94). After transplantation was observed an increased risk of cancer, especially skin (82%), lymphoproliferative diseases (between 1 and 11%) (non-Hodgkin lymphoma, Hodgkin’s disease, leukemia) and Kaposi’s sarcoma (6%) (94-98). Other cancers that have more incidence than general population are lip, tongue, mouth, salivary gland, esophagus, stomach, colon, anus, liver, gallbladder, lung, connective and soft tissue, vulva, cervix, penis, eye, thyroid and cancer of unknown origin (10, 99). The incidence of tumors that often trigger the IRCT (myeloma, renal and urinary tract cancer) is increased in patients with renal failure during dialysis and after transplantation (10).

Mortality associated with cardiovascular events remains the leading global cause of death after transplantation (94, 100). Analyzing the cause of death in terms of time since the transplant, the first year the main cause are infections, after this moment the mortality associated with the development of cancer is ranked first (100). The mean time between transplantation and the appearance of the neoplasm is 9.4 years (10).

Screening is advised in search of renal, colorectal, prostate, cervical and breast cancer in all
candidates, and especially if they are over 50 years of age. Periodic abdominal ultrasound is indicated and PSA determination with rectal digital examination in males over 50 years of age, on an annual basis. Women in turn are to undergo cervical cytology with gynecological exploration and mammography on a regular basis (101). Since skin cancer is the most frequent neoplasm in transplanted patients, an exhaustive dermatological study is required before inclusion of the patient on the transplant waiting list (1). The plain chest X-ray study performed as part of the preoperative workup will help to discard possible lung cancer (1). Some time ago it was advisable to perform colorectal cancer screening by faecal occult blood test and colonoscopy. Recent studies have shown no increased incidence of this neoplasm among the ESRD population, so it is recommended to use the same criteria to indicate a colonoscopy as in the general population (102).

Despite both the high risk in this population group and the potential benefits, some authors question the role of generalized screening (103). In this context, it would be prudent to conduct general screening, to be expanded according to the patient antecedents (urine cytology in the case of microhematuria, nephropathy due to analgesics, antecedents of urothelial carcinoma, or previous treatment with cyclophosphamide) (1, 104).

Regarding the waiting time for patients with neoplasms before entering the transplant waiting list, a number of registries are available (American Society of Transplant Physicians and European Best Practice Guidelines for Renal Transplantation) that stratifies waiting time between 1-5 years according to the type of tumor (40, 105) (Table 8). The Cincinnati Transplant Tumor Registry (CTTR) (106, 107) offers some additional data in reference to the decision taking process. In effect, the waiting time depends on the type of tumor, its TNM stage and the risk of recurrence after treatment. The mentioned registry considers that there are tumors that do not imply an increased risk for transplant candidates (e.g., incidental renal cancer or skin basal cell tumors), while others are able to reactivate even after prolonged remission periods (e.g., melanoma, cutaneous epidermoid carcinoma, breast cancer or myeloma) (108).

The CTTR finds no evidence to suggest that transplantation alters the rate and timing of recurrence in any of the types of neoplasm. A prolonged waiting

### TABLE V. IMAGING STUDIES IN THE EVALUATION OF CANDIDATES FOR KIDNEY TRANSPLANTATION.

<table>
<thead>
<tr>
<th>Pretransplantation Imaging Explorations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain chest X-rays</td>
<td>Forms part of the conventional preoperative workup. Screening for lung cancer and pulmonary tuberculosis</td>
</tr>
<tr>
<td>Plain abdominal X-rays</td>
<td>Study of vascular calcifications in aorto-iliac arterial territory</td>
</tr>
<tr>
<td>Peripheral artery echo-Doppler and/or abdominopelvic CAT with vascular reconstruction</td>
<td>In the presence of cardiovascular risk factors (see Table 2). Presence of vascular calcifications on plain abdominal X-rays. Antecedents of pelvic radiotherapy. Signs or symptoms of peripheral vascular disease</td>
</tr>
<tr>
<td>Angiography</td>
<td>Suspected occlusive vascular disease with a view to starting pretransplantation treatment / revascularization</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>For all patients as part of urinary tract evaluation (postmicturition residue measurement, evaluation of polycystic kidneys, etc.). Diabetics with suspected cholelithiasis</td>
</tr>
</tbody>
</table>
time reduces relapse among the transplanted patient cohort, but does not lessen relapse among the patients that have been excluded from transplantation. The decision regarding waiting time and patient inclusion on the transplantation waiting list is to be taken on an individualized basis, according to the prognosis with or without transplantation (1, 106). In patients who develop post-transplant neoplasia seems safer to use a mTOR inhibitor sirolimus as monotherapy or in combination with low doses of a calcineurin inhibitor, as evidence suggests it may increase survival in some cases (94, 109).

a) Urogenital tumors:

1) Renal cancer: the second frequency urogenital tumor diagnosed after transplantation is the renal cell carcinoma, being the papillary variety the most frequent histological pattern (101, 110). These tumors are more frequent among patients on dialysis than in the general population (3.3 and 9.9 times more frequent) (111). Acquired polycystic renal disease in patients on dialysis implies an increased risk of renal cancer (90, 112). Patients with autosomal dominant polycystic kidney disease (ADPKD) have increased risk of renal cancer, although it is not recommended to perform a prophylactic bilateral nephrectomy, particular attention to monitoring these patients with a close follow up protocol should be established (113).

Tumors that are incidentally detected in patients with ESRD have a very low recurrence rate after transplantation (1%), while symptomatic renal cancer has a high relapse rate (27%) (114). Screening based on abdominal ultrasound is indicated, though there is no consensus as to the periodicity of such exploration (90, 101). Surgery is the treatment of choice, and laparoscopic radical nephrectomy reduces morbidity and accelerates recovery compared with conventional open surgery (115).

2) Bladder cancer: the urogenital tumor most frequently diagnosed after transplantation is the transitional cell carcinoma of the bladder (110). These tumors are between 1.4 and 4.8 times more frequent in patients receiving renal replacement therapy than in the healthy population (5). The risk is greater among patients with ESRD secondary to toxic agents, infections, or obstructive urological disorders (111). Dialysis patients and those transplanted have more frequently aggressive forms of bladder cancer, including squamous and micropapillary variant and more likely to present with muscle-invasive disease (104, 116). The risk of non-infiltrating bladder tumor (including carcinoma in situ) recurrence after transplantation is very low (5), while in the case of

<table>
<thead>
<tr>
<th>PHYSICAL EXAMINATION</th>
<th>FINDINGS</th>
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<tbody>
<tr>
<td>Abdomen</td>
<td>Register the presence of palpable masses, enlarged organs and scars from previous surgery</td>
</tr>
<tr>
<td>Genitals</td>
<td>Exploration of penis and testicles. Rectal digital exploration in males &gt;50 years or &gt;45 years with risk factors. Genital exploration and gynecological cytology in women</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Exploration to identify poor peripheral perfusion, chronic venous insufficiency, ulcers or wounds. Palpation of pulses and auscultation in search of murmurs</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Evaluation of technical viability of the graft according to body conformation of the patient. In general, obese patients (BMI &gt;35 kg/m2) are to be referred to the Service of Endocrinology to adopt weight-lowering measures before surgery</td>
</tr>
</tbody>
</table>
infiltrating bladder cancer the relapse rate is 29%, with a mortality rate of 38% (107). Screening of the risk population and of heavy smokers is indicated, as well as of those individuals with a history of schistosomiasis or treatment with cyclophosphamide (5, 104). Should not overlook the presence of microhematuria or monosymptomatic hematuria (104).

3) Testicle cancer: there is no evidence that ESRD patients have a higher incidence of these tumors than the general population (5). Nevertheless, a thorough physical examination is recommended during the pretransplantation workup phase, including the genitals. The testicle tumor recurrence rate after transplantation is 5% (107).

4) Penile cancer: it has shown an increased incidence of this cancer in the transplant population, probably related with the human papilloma virus (10). As with testicular cancer, a proper physical examination in pre-transplant assessment will identify suspicious lesions.

5) Prostate cancer: ESRD and hemodialysis (HD) do not seem to alter PSA value in the detection of prostate cancer, neither influence on the PSA levels (117, 118). It is estimated that 1 in 10 men will suffer from prostate cancer at some point in their lives (119). There have been no reports of increased prostate cancer incidence among the ESRD population in replacement therapy or after renal transplantation (10, 111, 119), although the mean age of these patients causes many of them to belong to the risk group for developing this malignancy (90, 120). At present there are no universally accepted recommendations regarding PSA testing and prostate cancer screening in the general population (117). We recommend a yearly DRE and PSA determination for all transplant candidates over 50 years of age, and even earlier in those patients with familiarly background of prostate cancer so they can benefit from early diagnosis, despite the disagreement over the screening population in this type of tumor (1, 5, 90, 117). There is little information about how the immunosuppression affects on the development and progression of prostate cancer, so the approach

| TABLE VII. INDICATIONS OF NEPHRECTOMY IN RELATION TO NATIVE KIDNEYS PRIOR TO TRANSPLANTATION (1, 2, 5). |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------|
| **DISEASE**                                  | **NEPHRECTOMY**                                                                                 |
| Dominant autosomal                           | Uni- or bilateral before or during transplantation, in the case of:                            |
| polycystic kidney disease                    | Insufficient space for graft.                                                                   |
|                                              | Cyst complications: infection, rupture with / without hematuria, pain, abdominal distension    |
| Arterial hypertension refractory to clinical treatment | Bilateral.                                      |
|                                              | Usually requires less medication for hypertension control                                      |
| Chronically infected kidney/s                | According to affected side                                                                      |
| Suspected renal or urothelial cancer          | Uni- or bilateral                                                                               |
| Lithiases                                    | Nephrectomy in case of infective lithiases or in case of possible secondary infection           |
| Severe proteinuria (>10 g/24 h) due to nephrotic syndrome (particularly in pediatric patients) | Uni- or bilateral, depending on severity                                                       |
| Persistence of anti-glomerular basal membrane antibodies | Bilateral                                                                                     |
| Infected or severe (grade IVV) vesicoureteral reflux, infected or lithiastic obstructive megaureter | According to affected side                                                                      |
to this pathology in transplant candidates should be aggressive (117, 119). Treatment options for prostate cancer in renal transplant candidate population are comparable to those for the general population (119). Patients treated for prostate cancer show have an overall recurrence rate after transplantation of about 18% with a cancer-specific mortality of about 30% (107, 121). Time between treatment of prostate cancer and inclusion on the waiting list is variable and depends on the stage at diagnosis, it is strongly recommend waiting at least two years in stages I-II and at least five in stage III (106, 121).

**CONCLUSION**

Kidney transplantation is the best treatment renal function replacement. While the number of organs available for transplantation is limited, the number of patients with ESRD is increasing. The study of renal transplant candidate is essential to improve graft and patient survival. The ESRD patient usually has a complex medical history and comorbidities that may influence on the success of the surgery.

A careful global medical, urological and oncological study is essential for a complete and accurate pretransplant assessment. Detect and correct potentially dangerous situations for the evolution of transplantation reduces the risk associated with this procedure. This evaluation must be conducted by a multidisciplinary team, in which the urologist should be involved in determining how it will be primarily responsible for the success of the surgery.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)


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