ORIGINAL ARTICLE
ARTIGO ORIGINAL

# Direct costs associated with lupus nephritis management in the Private Healthcare System in Brazil: an expert panel perspective

## *Custos diretos associados ao manejo da nefrite lúpica no Sistema de Saúde Privado no Brasil: uma perspectiva segundo painel de especialistas*

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**DOI:** 10.21115/JBES.v14.n3.p232-246

**Keywords:**
lupus nephritis, costs, immunosuppression, corticosteroids, kidney transplant, dialysis

## ABSTRACT

**Objective:** To estimate direct medical costs of lupus nephritis (LN) in the Brazilian private healthcare system. **Methods:** An expert panel of five specialists were convened to discuss health resource usage in LN patient management. The discussion included diagnosis, treatment, and disease monitoring, including dialysis and kidney transplantation. Unit costs (in BRL) were obtained from public sources, and an estimation of 1-year costs was conducted. **Results:** Approximately 76.0% of patients with LN undergo kidney biopsy, of which 48.1% present with LN classes III–IV and 21.4% have class V. Around 67.5% of patients with LN classes III–IV experience an average of four renal flares annually. Overall, 20.3% of patients present refractory LN, and 10.3% have end-stage kidney disease (ESKD), requiring dialysis and kidney transplantation. Estimated total weighted annual costs per patient were BRL 115,824.81 for LN classes III–IV, BRL 85,684.79 for LN class V, BRL 115,594.98 for refractory LN; and BRL 325,712.88 for ESKD. The main annual cost driver for LN classes III–IV was renal flares (BRL 60,240.41; 52.0%) and dialysis for LN class V (BRL 31,128.38; 36.3%). **Conclusions:** Total direct costs increase when LN progresses to ESKD. Although it is challenging to improve the diagnosis, identification of the disease at an early stage, together with rapid initiation of treatment, are fundamental elements to optimize results, potentially reducing costs to the system and the impact of disease burden and quality of life on patients.

**Palavras-chave:**
nefrite lúpica, custos, imunossupressão, corticosteroides, transplante renal, diálise

## RESUMO

**Objetivo:** Estimar os custos médicos diretos da nefrite lúpica (NL) no sistema suplementar de saúde brasileiro. **Métodos:** Um painel de cinco especialistas foi estruturado para discutir o uso de recursos em saúde no manejo de pacientes com NL. Nesta discussão, incluíram-se o diagnóstico, o tratamento e o monitoramento da doença, contemplando também diálise e transplante renal. Os custos unitários foram obtidos de fontes públicas e os resultados expressos em custo anual. **Resultados:** Aproximadamente 76,0% dos pacientes com NL são submetidos à biópsia renal, sendo 48,1% com NL de classes III-IV e 21,4% de classe V. Cerca de 67,5% dos pacientes com classes III-IV apresentam, aproximadamente, quatro *flares* renais anuais. No geral, 20,3% dos pacientes apresentam NL refratária e 10,3% desenvolvem doença renal terminal (DRT), necessitando de diálise e

**Received on:** 28/10/2022.**Approved for publication on:** 28/11/2022.
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**Institution where the work was performed:** IQVIA Brasil, São Paulo, SP, Brazil.
**Funding:** This work was funded by GSK (GSK 217650; Rio de Janeiro, RJ, Brazil).
**Prior presentations**: Some parts of this work have previously been presented at ISPOR 2022.
**Conflict of interest:** DOS, ND, MRG, and GB are employees of GSK. ND, MRG, and GB own stocks/shares in GSK. BK and DK are employees of IQVIA and conducted the study on behalf of GSK. OAM has received speaker fees from AbbVie, AstraZeneca, Boehringer Ingelheim, GSK, Janssen, and Novartis, all unrelated to this manuscript. AH reported no conflict of interest.
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transplante renal. O custo ponderado anual estimado por paciente foi de R$ 115.824,81 para NL de classes III-IV, R$ 85.684,79 para classe V, R$ 115.594,98 para NL refratária e R$ 325.712,88 para DRT. O principal fator para incremento dos custos anuais para NL de classes III-IV foram os *flares* renais (R$ 60.240,41; 52,0%) e, na classe V, a diálise (R$ 31.128,38; 36,3%). **Conclusões:** Há um incremento dos custos diretos da NL na progressão para DRT. Embora seja desafiador melhorar o diagnóstico, a identificação da doença em uma fase precoce, aliada ao tratamento iniciado de forma célere, são elementos fundamentais para otimizar os resultados, potencialmente reduzindo os custos ao sistema e o impacto da carga da doença e qualidade de vida dos pacientes.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that affects several organs over time, with progression typically comprising periods of activity and remission (Anders *et al.*, 2020, Ruperto *et al.*, 2011). Renal inflammatory involvement, known as lupus nephritis (LN), is one of the most severe manifestations of the disease and is associated with high morbidity and mortality (Anders *et al.*, 2020). It is estimated that 40% of patients with SLE develop LN, and 5–20% progress to end-stage kidney disease (ESKD; within ten years of diagnosis), requiring dialysis and even kidney transplantation (Anders *et al.*, 2020).

In Brazil, with data generally scarce and limited to the south and southeast regions of the country, studies indicate that the incidence of SLE is 4.2–8.7 cases per 100,000 inhabitants per year (Klumb *et al.*, 2021). As for prevalence, it is estimated around 150,000–300,000 patients with SLE (Klumb *et al.*, 2021). As approximately 40% of patients with SLE develop LN (Morales *et al.*, 2021), up to 120,000 individuals may have LN in Brazil. In terms of mortality, it is estimated that patients with LN are at a 6-fold higher risk of death than the general population, particularly when developing ESKD, when this value rises to about 26 times (Yap *et al.*, 2012). To give an idea of this risk, a patient with LN who develops ESKD has a risk of death up to twice as high compared to a scenario in which, instead of ESKD, the patient developed cardiovascular disease or neoplasia (Yap *et al.*, 2012).

LN is one of the most common causes of using high doses of corticosteroids and immunosuppressants. It is associated with increased hospitalization rates and is one of the main factors related to mortality in SLE patients (Klumb *et al.*, 2015). Based on national data comparing individuals on dialysis with and without SLE, patients with SLE had a lower survival rate at five years (73% vs. 83%). It was even lower when the patient experienced high disease activity (only 17% when non-renal Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score is above 8) (Ribeiro *et al.*, 2013).

LN is classified according to different histological presentations, ranked from I to VI, with clinical manifestations ranging from nephrotic syndrome to nephrotic syndrome associated with loss of renal function (Anders *et al.*, 2020). This classification is based on the prognosis of the disease; classes I and II do not present an immediate risk of progression to ESKD, while classes III, IV, and V are under this risk (Anders *et al.*, 2020). LN class VI already represents a situation of significant chronic damage and is linked to ESKD. It is important to note that the increasing numbers do not indicate a progressively more severe condition. Specifically, classes III and IV, characterized by focal and diffuse proliferative renal inflammatory involvement, respectively, are strongly associated with an irreversible loss of nephrons that reduce kidney lifespan and, consequently, generate a greater risk of death (Anders *et al.*, 2020, Mejía-Vilet *et al.*, 2016, Romagnani *et al.*, 2017, Yap *et al.*, 2012). Thus, it is evident that precise and early diagnosis is vital for timely therapeutic initiation (Anders *et al.*, 2020, Mejía-Vilet *et al.*, 2016, Romagnani *et al.*, 2017).

Kidney flares are reactivations of kidney disease characterized by a sudden increase of proteinuria and/or serum creatinine levels, the onset of abnormalities in urinary sediment, or decreased creatinine clearance (glomerular filtration rate) (Sprangers *et al.*, 2012). Flares can also be compared to an episode of acute renal injury, resulting in irreversible kidney damage and accelerating progression to ESKD (Anders *et al.*, 2020). Thus, the effects of kidney flares should be promptly mitigated by appropriate therapeutic management, often guided by results of new renal biopsy but also done empirically, observing the characteristics of the clinical condition aided by complementary laboratory tests, with the intensification of corticosteroid therapy and immunosuppression associated with response monitoring. Cases of negative response to this treatment may indicate refractory LN *(*Klumb *et al.*, 2015*,* Sprangers *et al.*, 2012).

Renal biopsy is the current gold standard for diagnostic confirmation of LN (Anders *et al.*, 2020). In addition, in cases that are refractory to treatment or have relapsed, a renal biopsy can help identify differential diagnoses and the progression of renal damage (Anders *et al.*, 2020, Fanouriakis *et al.*, 2020, Klumb *et al.*, 2021). However, the difficulty of access to specialized pathology services in Brazil, added to the high cost and risks of complication inherent to the invasive nature of this procedure, restrict the use of this technique for confirmation and follow-up of the disease (Klumb *et al.*, 2021).

In the absence of a biopsy, no other tests accurately provide histological information (Klumb *et al.*, 2021, Klumb *et al.*, 2015). Only a biopsy can detect non-lupus conditions that may be happening concomitantly, such as microangiopathy associated with antiphospholipid antibody syndrome and acute tubular necrosis (Bustamante *et al.*, 2022). Alternatively,

the literature points to the use of biomarkers such as specific urinary molecules only available at the research level, complements (C3 and C4), anti-nucleosome antibodies, anti-dsDNA, and anti-C1q to infer the histological class or measure disease activity (Fanouriakis *et al.*, 2020, Klumb *et al.*, 2021). However, the availability of these tests is also variable in Brazil (Klumb *et al.*, 2021).

In addition, the scarcity of data on costs involved in managing different histological classes of LN makes it challenging to understand the actual economic impact of the disease in Brazil. Internationally, the reported financial burden of LN is substantial, representing an annual cost up to 6-fold higher than in patients without SLE (USD 33,472 vs. USD 5,347; p<0.001; 2009) (Furst *et al.*, 2013) or up to 2.5-fold higher than in patients with SLE but without LN (USD 30,652 vs. USD 12,029; p<0.001; 2008) (Pelletier *et al.*, 2009). The cost of renal flares has an essential contribution in this respect, given that a single severe flare (including renal flares) can represent an incremental direct cost of more than USD 17,000 per flare (Garris *et al.*, 2013).

Given the above, this study (GSK 217650) was developed to describe, from the perspective of the Brazilian Private Healthcare System, the healthcare resources used, and costs associated with different stages of treatment of LN patients based on the experience of specialists in the area.

## Methods

A panel of experts was assembled to discuss the use of healthcare resources in managing LN patients. Recruitment of specialists was conducte5d in August 2021, comprising five rheumatologists and nephrologists who had seen patients with LN in private health institutions in Brazil over the last 12 months before recruitment. A contracted company selected physicians, and the recruitment process was double-blinded for the study sponsor and the participating specialists.

The first stage of the study was the development of an objective questionnaire based on clinical practice guideline recommendations and publications relevant to LN; to identify healthcare resources needed for diagnosis, prevention, response and monitoring, drug therapy, renal flares, dialysis, and kidney transplantation. The use of resources was segmented according to the LN treatment profile, considered as classes III, IV, and V, refractory LN, and ESKD. This questionnaire was sent to the specialists so they could return it completed before the panel, thus enabling data collection from their clinical practice concerning managing patients with LN in an individualized manner.

The therapies considered in this questionnaire included immunosuppression and corticosteroid therapy, each with a period of induction and maintenance, also including adjuvant therapy for comorbidities (antihypertensives, statins, anticoagulants, and supplementation with calcium and vitamin D), hydroxychloroquine, prophylaxis for tuberculosis, *Pneumocystis jiroveci* pneumonia, and parasitosis. Adjuvant therapies were used in all treatment profiles except for ESKD, in which no specific treatment was reported in addition to indications for dialysis and kidney transplantation. Drug dosage and the use of biopsy in the diagnosis were also explored in the questionnaire. In this study, it was already considered that the patient had a diagnosis of SLE before finding LN (Anders *et al.*, 2020, Centers for Medicare & Medicaid Services, 2019, Fanouriakis *et al.*, 2020, Gorham *et al.*, 2019, Hahn *et al.*, 2012, Klumb *et al.*, 2015, Silva *et al.*, 2016).

After the questionnaire stage and based on the answers received, a discussion guide was prepared during the expert panel session, comprising quantitative and qualitative elements not addressed in the questionnaire. This guide followed the same categories previously addressed, complementing the data from the previous stage of the questionnaire, and directing the focus of the discussions to capture better healthcare resource utilization. The panel discussion took place online in August 2021 and lasted 2 hours.

Finally, the data collected from the questionnaire and complemented by the expert panel were compiled and analyzed in Microsoft® Excel. For the analysis of micro-costing, the reported average use of each resource and its respective unit cost was considered. Thus, the total weighted cost per patient was estimated in an annual time horizon, according to the individual LN class. Additionally, the total costs without weighting are reported in parentheses after the weighted cost, representing the maximum cost a patient could achieve if all resources were used by 100% of patients.

### *Costs*

Unit costs (in BRL) were obtained from public sources. For tests and medical procedures, the Brazilian Hierarchical Classification of Medical Procedures (CBHPM) was consulted, with data from 2020 (Associação Médica Brasileira, 2020); for drug costs, the ex-factory price plus 18% tax from the list of the Drug Market Regulation Chamber (CMED) was used with data from April 2022 (Câmara de Regulação do Mercado de Medicamentos (CMED), 2021). The required doses were adjusted according to the therapeutic guidelines or respective package inserts of the products. The costs of complications in the hospital setting, including pneumonia and post-transplant complications, were estimated according to the Supplementary Health Information Exchange Data (DTISS), with 2016 data adjusted according to the Broad National Consumer Price Index (IPCA) from June 2016 to August 2021 (Instituto Brasileiro de Geografia e Estatística (IBGE), 2021). Finally, the costs of hospitalization, intensive care unit daily rates, and daily rates for hospitalization for organ transplantation were based on the costs reported for 2020 by the operator Planserv, which operates in the coverage of public servants in Bahia state (Planserv, 2020).

### *Dosage of therapies*

For the defrayal of therapies over a year, a premise was adopted that the patient would be under an induction period of about three months, during which there would be preservation or improvement of renal function with a 25% reduction in proteinuria, according to the guidelines of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA–EDTA) (Fanouriakis *et al.*, 2020). After a response during that period, the patient would proceed to the maintenance period and be treated accordingly for the remaining nine months of the year. The treatments used in each period were adjusted according to the dosages in the package insert or treatment guidelines for the respective duration, whether induction or maintenance, totaling one year of treatment.

### *Use of resources for kidney transplantation*

No studies from the Brazilian Private Healthcare System perspective could estimate the use of resources involved in kidney transplantation and its subsequent defrayal. Thus, we chose to seek the associated resources from a national study by Silva *et al.* (2016), which measured the economic impact of kidney transplantation from the public health perspective (Silva *et al.*, 2016).

The procedures used in each kidney transplant modality reported in the study, with kidney grafts from either a living or dead donor (Silva *et al.*, 2016), were consulted at the CBHPM, plus a typed follow-up for this purpose ("Clinical follow-up of renal transplantation in the hospitalization period [post operative up to 15 days]") under code 20201010. The panel of experts validated these procedures according to the practice in the Brazilian Private Healthcare System. In this topic of defrayal, it was considered that the patient would receive the transplant on day one, and the cost would be related to the procedure, follow-up, immunosuppression, possible complications, and graft failure (requiring dialysis until the end of the period).

## Results

### *Diagnosis*

It was identified that approximately 76% of patients seen in the clinical practice of the interviewed physicians, considering the retrospective period of 12 months, were diagnosed by renal biopsy. Regarding the distribution of patients' profiles based on the recommended management of LN, 48.1% were classified as classes III and IV, 21.4% as class V, 20.3% as refractory LN, and 10.3% as ESKD. The experts reported that, for the diagnosis of LN, all patients are referred to outpatient visits and creatinine clearance tests, anti-dsDNA autoantibodies, urinalysis of isolated samples, and microscopic examination of urine sediment. Approximately 90% of patients underwent complete blood count and serum complement dosage (C3 and C4), and 96.0% underwent 24-hour urinalysis for dosing proteinuria. For differential diagnosis, physicians reported requesting the use of urine culture, lupus anticoagulant, and anticardiolipin to 75.0%, 70.0%, and 80.0% of patients, respectively. For the diagnosis stage, the weighted average annual cost per patient, regardless of the LN profile, totaled BRL 2,563.66 and could reach the maximum of BRL 6,528.70 (Table 1).

### *Infectious prophylaxis*

The responses indicated that all patients were examined with chest X-rays. Other tests included the tuberculin test (PPD) in 66.0% of patients, parasitic infection research in 32.0%, and proto-parasitological stool test in 20.0% of patients. Drugs used to perform infectious prophylaxis were isoniazid (60.0%) or rifampicin for tuberculosis (60.0%), albendazole for parasitosis (40.0%), sulfamethoxazole associated with trimethoprim (20.0%) for pneumocystosis and ivermectin (20.0%). The weighted average cost per patient totaled BRL 542.21 (and can reach BRL 1,787.42) per year, regardless of the LN classification (Table 1).

### *Response assessment and monitoring*

At least 90% of patients underwent consultations, isolated samples of urinalysis, and creatinine clearance every six weeks over one year. A complete blood count was recommended for all patients approximately every nine weeks. Microscopic examination of urine sediment was performed in all patients every 13 weeks, while serum albumin was reported in 80% of patients roughly every 17 weeks. Other tests in 40% of patients included serum complement dosage (C3 and C4) and anti-dsDNA autoantibodies, with requests reported once a year. The total weighted cost per patient in one year was BRL 3,162.27 and can reach BRL 3,274.51 (Table 1).

### *Drug treatment*

#### Adjuvant therapy (considered for all LN cases)

Adjuvant therapy costs were already included in the total reported cost for each LN classification. Adjuvant therapy highlighted hydroxychloroquine in 100% of patients, with calcium and vitamin D supplementation in 87.5% and 95.0%, respectively. Rosuvastatin was reported for 44.0% and losartan for 41.3% of patients. In addition to these, other drugs used in more than 30% of patients include enalapril (32.0%), atorvastatin (31.5%), and valsartan (31.3%). Regardless of LN class, the total weighted cost of adjuvant therapy was BRL 4,035.45 (and can reach up to BRL 10,845.55) per patient/year (Table 2).

#### LN classes III and IV

During the induction period, the immunosuppressant most frequently used was cyclophosphamide (CYC; 66.0%), followed by mycophenolate mofetil (MMF; 46.0%) and azathioprine (AZA; 16.0%). Pulse therapy with methylprednisolone

and oral prednisone was reported in 96.0% of LN patients. During the maintenance period, MMF was the most used immunosuppressant (50.0%), followed by AZA (48.0%) and cyclosporine (CsA; 22.0%). Oral prednisone was reported in 95.0% of patients (Table 3). The total weighted cost of the therapies + adjuvants for patients with LN of histological subtypes III and IV was BRL 18,187.87 (and can reach up to BRL 44,787.06) per year (Table 1).

### LN class V

During the induction period, CYC was the most used immunosuppressive agent (54.0%), followed by MMF (41.0%), AZA (15.0%), and CsA (4.0%). Pulse therapy with methylprednisolone was present in 90.0% of patients, while oral prednisone was reported in 62.0% of LN patients. In maintenance, AZA presented the highest percentage of use (68.0%), followed by MMF (48.0%) and CsA (4.0%). Oral prednisone was present in 56.0%. The use of rituximab (RTX) was observed in about 20.0% of patients (Table 3). The total weighted cost per patient with therapies + adjuvants for class V totals BRL 18,168.06 (and can reach up to BRL 69,695.28) per year (Table 1).

### Refractory LN

In the case of refractory LN, the diagnostic investigation to confirm refractoriness was also requested. It indicated that renal biopsy is used in only 12.5% of cases, accompanied by other tests such as SLE activity tests (76.0%) and urinary tract ultrasound (25.0%; Table 3).

For induction, the most common immunosuppressants were CYC, MMF, and tacrolimus, used in 44.0%, 42.0%, and 16.0% of LN patients, respectively. Pulse therapy with methylprednisolone and oral prednisone were each reported in 76.0% of patients with this disease. Unlike the other treatments, RTX was widely used and reported in 68.0% of patients. For maintenance, MMF led the immunosuppressants (50.0%), followed by AZA (40.0%), and tacrolimus (12.0%). Oral prednisone and rituximab use were reported in 76.0% and 52.0% of patients, respectively, during maintenance (Table 3).

**Table 1.** Summary of weighted costs per treatment profile of LN patients

| Category | Classes III and IV | Class V | Refractory LN | ESKD |
|---|---|---|---|---|
| Diagnosis | BRL 2,563.66 | BRL 2,563.66 | BRL 2,563.66 | BRL 2,563.66 |
| Prophylaxis | BRL 542.21 | BRL 542.21 | BRL 542.21 | BRL 542.21 |
| Response and monitoring | BRL 3,162.27 | BRL 3,162.27 | BRL 3,162.27 | BRL 3,162.27 |
| Therapy + adjuvants | BRL 18,187.87 | BRL 18,168.06 | BRL 55,887.20 | BRL - |
| Renal flares | BRL 60,240.41 | BRL 30,120.21 | BRL 22,311.26 | BRL - |
| Dialysis | BRL 31,128.38 | BRL 31,128.38 | BRL 31,128.38 | BRL 239,490.15 |
| Transplantation | BRL - | BRL - | BRL - | BRL 79,954.60 |
| **Total** | **BRL 115,824.81** | **BRL 85,684.79** | **BRL 115,594.98** | **BRL 325,712.88** |

ESKD: end-stage kidney disease; LN, lupus nephritis.

**Table 2.** Weighted cost of adjuvant treatment reported per LN patients (for all LN classes)

| Regimen | Frequency | Number of packs | Weighted cost |
|---|---|---|---|
| Hydroxychloroquine | 100.0% | 6 | BRL 783.12 |
| Enalapril | 32.0% | 24 | BRL 47.08 |
| Captopril | 20.8% | 24 | BRL 143.42 |
| Ramipril | 24.5% | 2 | BRL 82.55 |
| Losartan | 41.3% | 6 | BRL 54.43 |
| Valsartan | 31.3% | 12 | BRL 142.91 |
| Simvastatin | 21.5% | 24 | BRL 80.44 |
| Atorvastatin | 31.5% | 24 | BRL 211.15 |
| Rosuvastatin | 44.0% | 24 | BRL 380.16 |
| Aspirin | 23.0% | 11 | BRL 65.15 |
| Rivaroxaban | 26.0% | 36 | BRL 525.28 |
| Apixaban | 22.0% | 36 | BRL 704.88 |
| Calcium supplementation | 87.5% | 6 | BRL 267.23 |
| Vitamin D supplementation | 95.0% | 24 | BRL 547.66 |
| Total weighted cost | | | **BRL4,035.45** |

LN: lupus nephritis.

**Table 3.** Weighted cost of treatment reported for LN classes III and IV, class V and refractory.

| Regimen | Frequency | Number of packs | Weighted cost |
|---|---|---|---|
| **LN CLASSES III AND IV** | | | |
| **Induction** | | | |
| Cyclophosphamide | 66.0% | 2 | BRL 86.39 |
| Mycophenolate mofetil | 46.0% | 54 | BRL 3,408.79 |
| Azathioprine | 16.0% | 5 | BRL 82.00 |
| Pulse therapy with methyl prednisolone | 96.0% | 10 | BRL 144.00 |
| Oral prednisone | 96.0% | 21 | BRL 192.53 |
| **Maintenance** | | | |
| Azathioprine | 48.0% | 14 | BRL 688.80 |
| Mycophenolate mofetil | 50.0% | 108 | BRL 7,410.42 |
| Cyclosporine | 22.0% | 18 | BRL 2,012.47 |
| Oral prednisone | 95.0% | 14 | BRL 127.02 |
| **Total weighted cost** | | | **BRL 14,152.42** |
| **LN CLASS V** | | | |
| **Induction** | | | |
| Cyclophosphamide | 54.0% | 2 | BRL 70.69 |
| Mycophenolate mofetil | 41.0% | 45 | BRL 2,531.89 |
| Azathioprine | 15.0% | 5 | BRL 76.88 |
| Cyclosporine | 4.0% | 18 | BRL 365.90 |
| Pulse therapy with methyl prednisolone | 90.0% | 6 | BRL 81.00 |
| Oral prednisone | 62.0% | 18 | BRL 106.58 |
| **Maintenance** | | | |
| Mycophenolate mofetil | 48.0% | 81 | BRL 5,335.50 |
| Azathioprine | 68.0% | 14 | BRL 975.80 |
| Cyclosporine | 4.0% | 18 | BRL 365.90 |
| Oral prednisone | 56.0% | 11 | BRL 58.83 |
| Rituximab | 20.0% | 20 | BRL 4,163.64 |
| **Total weighted cost** | | | **BRL 14,132.61** |
| **REFRACTORY LN** | | | |
| **Diagnostic confirmation** | **Frequency** | | **Weighted cost** |
| Urinary tract ultrasound | 25.0% | | BRL 76.91 |
| Renal biopsy | 12.5% | | BRL 143.12 |
| Consultation with specialist | 25.0% | | BRL 56.23 |
| Tests of SLE activity | 76.0% | | BRL 62.85 |
| **Treatment regimen** | **Frequency** | **Number of packs** | **Weighted cost** |
| **Induction** | | | |
| Cyclophosphamide | 44.0% | 2 | BRL 57.60 |
| Tacrolimus | 16.0% | 23 | BRL 774.60 |
| Mycophenolate mofetil | 42.0% | 54 | BRL 3,112.38 |
| Pulse therapy with methyl prednisolone | 76.0% | 10 | BRL 114.00 |
| Oral prednisone | 76.0% | 21 | BRL 152.42 |
| Rituximab | 68.0% | 30 | BRL 21,234.56 |
| **Maintenance** | | | |
| Mycophenolate mofetil | 50.0% | 108 | BRL 7,410.42 |
| Azathioprine | 40.0% | 14 | BRL 574.00 |
| Tacrolimus | 12.0% | 69 | BRL 1,742.86 |
| Oral prednisone | 76.0% | 14 | BRL 101.61 |
| Rituximab | 52.0% | 30 | BRL 16,238.20 |
| **Total weighted cost** | | | BRL 51,851.74 |

LN: lupus nephritis; SLE: systemic lupus erythematosus.

For this treatment profile, the total weighted cost of identification and reported therapies + adjuvants was BRL 55,887.20 (and can reach up to BRL 118,706.81) per patient/year (Table 1).

### Renal flares

Renal flares varied according to histological subtype or LN treatment profile. For LN classes III and IV, it was reported that 67.5% of patients had an average of four episodes of renal flare per year. For LN class V, 45.0% of patients developed renal flares at a frequency of three episodes per year. When the disease became refractory, flare occurrences were reported in 37.5% of patients at an annual frequency of 2.7 episodes per year. In patients with ESKD, no flares were reported because the patient was either on dialysis or had received kidney transplantation, situations in which a flare rarely occurs.

It was also reported that approximately 20% of patients developed infections associated with renal flare, most commonly pneumonia, with a weighted cost estimated at BRL 695.05 (and can reach up to BRL 2,849.03).

In contrast to therapies, management of renal flares did not differ according to histological subtype or treatment profile, being managed with high doses of immunosuppressants and corticoids, including RTX in 31.3% of patients. Renal biopsy was reported in only 6% of patients in episodes of renal flare. The use of immunosuppressants such as CYC and MMF was reported in 50.0% of patients (Table 4).

Although the drug treatment was the same, the costs were different since they were adjusted based on the mean frequency and percentage of flares among LN classes (Table 4). The total weighted cost in a year was as follows (from highest to lowest): classes III and IV, class V and refractory LN, totaling, respectively, BRL 60,240.41 (BRL 310,425.58), BRL 30,120.21 (BRL 155,212.79) and BRL 22,311.26 (BRL 114,972.44) per year (Table 1).

### *Dialysis*

On average, it was reported that 23.7% of LN patients underwent dialysis. According to the panel of experts, 20.0% of patients with ESKD underwent peritoneal dialysis and 80.0% hemodialysis. It is noteworthy that patients of all classes were indicated for hemodialysis. On average, three hemodialysis sessions were performed per week, 4 hours per session, while for peritoneal dialysis, 8-hour sessions were performed every day (Table 5). Regarding medical resources, 90.0% of patients were submitted to consultation with a nephrologist, with an average frequency of 3 times a year (Table 5). Saline solution, heparin, and enalapril were most supplied (used in 100.0%, 90.0%, and 60.0% of patients, respectively), followed

**Table 4.** Use of resources and weighted cost of the initial approach of renal flares, therapy, and management of pneumonia associated with renal flare

| **Tests, consultations, or procedures** | | **Frequency** | **Weighted cost** |
|---|---|---|---|
| Renal biopsy | | 6.0% | BRL 68.70 |
| Potassium | | 20.0% | BRL 1.74 |
| Urea | | 20.0% | BRL 1.74 |
| **Subtotal** | | | **BRL 72.18** |
| **Treatment regimen** | **Number of packs** | **Frequency** | **Weighted cost** |
| Cyclophosphamide | 1 | 50.0% | BRL 32.73 |
| Mycophenolate mofetil | 54 | 50.0% | BRL 3,705.21 |
| Pulse therapy with methyl prednisolone | 60 | 92.5% | BRL 832.50 |
| Oral prednisone | 21 | 82.5% | BRL 165.45 |
| Rituximab | 40 | 31.3% | BRL 13,011.38 |
| Hemodialysis | 36 sessions | 6.3% | BRL 3,796.76 |
| **Subtotal** | | | **BRL 21,544.03** |
| | **Number of packs** | | **Weighted cost** |
| Pneumonia – ICD J18 – 20% of patients with renal flare | | | |
| Outpatient consultation | - | | BRL 61.32 |
| Chest X-ray | - | | BRL 25.15 |
| Blood culture (by sample) | - | | BRL 10.18 |
| Vancomycin | 84 | | BRL 441.84 |
| Other associated hospital costs | - | | BRL 156.56 |
| **Subtotal** | | | BRL 695.05 |
| **Total weighted cost** | - | | **BRL 22,311.26** |

ICD: International Classification of Diseases.

**Table 5.** Use of resources and weighted annual cost related to dialysis by indication and treatment profile

| Treatment profile | Frequency | Therapy of choice | Number of sessions per year | Weighted annual cost |
|---|---|---|---|---|
| Classes III and IV | 15.0% | Hemodialysis | 156 | BRL 29,868.23 |
| Class V | 15.0% | Hemodialysis | 156 | BRL 29,868.23 |
| Refractory LN | 15.0% | Hemodialysis | 156 | BRL 29,868.23 |
| ESKD | 80.0% | Hemodialysis | 156 | BRL 159,297.22 |
| ESKD | 20.0% | Peritoneal dialysis | 364 | BRL 70,613.09 |
| **Medicines and supplies** | **Frequency** | **Number of packs per procedure** | **Cost/annual weighted hemodialysis** | **Cost/annual weighted peritoneal dialysis** |
| Saline | 100.0% | 1 | BRL 1,340.04 | BRL 3,126.76 |
| Heparin | 90.0% | 1 | BRL 2,619.86 | BRL 6,113.02 |
| Insulin | 30.0% | 1 | BRL 607.93 | BRL 1,418.51 |
| Glucose 50% | 30.0% | 1 | BRL 280.80 | BRL 655.20 |
| Amiodarone | 30.0% | 1 | BRL 473.62 | BRL 1,105.10 |
| Chlorpheniramine | 5.0% | 1 | BRL 67.08 | BRL 156.52 |
| Hydralazine | 20.0% | 1 | BRL 207.79 | BRL 484.85 |
| Enalapril | 60.0% | 0.07 | BRL 38.25 | BRL 89.25 |
| Vancomycin | 5.0% | 4 | BRL 820.56 | BRL 1,914.64 |
| Subtotal | | | BRL 6,455.94 | BRL 15,063.85 |
| **Tests, consultations, or procedures** | | **Frequency** | **Annual frequency** | **Cost/year-of-charge** |
| Consultation with nephrologist | | 90.0% | 3 | BRL 607.23 |
| Venous access for dialysis | | 69.0% | 2 | BRL 1,337.88 |
| Fistula formation | | 31.0% | 1 | BRL 795.10 |
| **Subtotal** | | | | **BRL 2,740.20** |

ESKD: end-stage kidney disease; LN: lupus nephritis.

by insulin, glucose 50.0%, and amiodarone, each used in 30.0% of cases (Table 5). In addition, approximately 69.0% of patients underwent the central venous access procedure to receive dialysis (twice a year), and 31.0% underwent the access procedure by arteriovenous fistula (Table 5).

It was reported that all LN patients who received hemodialysis had up to 156 sessions per year. In comparison, patients with ESKD and an indication for peritoneal dialysis received up to 364 sessions per year. Considering that only ESKD patients are indicated for dialysis, the highest weighted cost belongs to this treatment profile, totaling BRL 239,490.15 (BRL 591,348.62) when the transplant is not received in one year. The other classes and treatment profiles display the same weighted value, totaling BRL 31,128.38 (BRL 203,660.86) per year (Table 1).

### *Kidney transplantation*

It was reported that about 10.3% of patients progressed to ESKD and had an indication for kidney transplantation. According to published data (Silva *et al.*, 2016), 90% of transplants performed received the organ from a deceased donor, while living donors provided the others. A 5% graft failure rate was reported in transplants, and they were managed by peritoneal dialysis (10%) or hemodialysis (90%) for the rest of the year at this micro-costing. The weighted costs for these procedures are provided in Supplementary Table 1. The weighted costs related to the pre-transplant tests and the transplants from deceased and living donors are described in Supplementary Tables 2, 3, and 4, respectively.

Soon after the transplantation, about 80% of patients were hospitalized due to complications related to cytomegalovirus (CMV). They were managed, in a hospital setting, with ganciclovir for 21 days. Other patients were hospitalized for other causes during the same period. In addition, a frequency of up to 4 rehospitalizations was reported in one year. Only the first occurred due to CMV in patients with this infection, and the remainder due to other causes (Silva *et al.*, 2016) (Supplementary Table 5). The immunosuppressants used post-transplantation were tacrolimus (75.0%), MMF (45.0%), AZA (3.8%), and sirolimus (1.3%). Almost all patients were monitored by a specialist twice a year, representing 98% of the cases (Supplementary Table 6). Thus, the total weighted cost

for kidney transplantation was BRL 79,954.60 (BRL 189,910.81), contemplating a scenario in which the patient received the transplant on the first day of the year (Table 1).

### *Total weighted cost per patient*

The summary of total costs per treatment profile is provided in Table 1. The total costs estimated in the first year for LN patients are, from the highest to the lowest, the following: BRL 325,712.88 (BRL 792,850.06) for ESKD, BRL 115,824.81 (BRL 570,464.13) for LN classes III–IV, BRL 115,594.98 (BRL 448,930.74) for refractory LN, and BRL 85,684.79 (BRL 440,159.56) for class V (Table 1). For ESKD and LN class V, dialysis was the main cost driver, totaling BRL 239,490.15 (73.5%; BRL 591.348.62) and BRL 31,128.38 (36.3%; BRL 203.660.86), respectively. For LN classes III–IV, renal flares were the main cost driver, with BRL 60,240.41 (52.0%; BRL 310,425.58). For refractory LN, the highest cost driver was therapies + adjuvants, consisting of immunosuppression, corticosteroid therapy, and adjuvants, totaling BRL 55,887.20 (48.3%; BRL 118,706.81) (Table 1).

## Discussion

The panel of experts assembled for this study allowed observation of a series of data on the use of healthcare resources and an approximate annual cost of LN patients in Brazil. Given the great difficulty in obtaining specific data due to the lack of national databases for SLE or LN and the low number of available studies on the burden of LN in Brazil, this analysis could help in the dimension of complexity and cost associated with this profile of patients, despite its limitations.

In an overall scenario, it is observed that the estimated annual cost per patient within the Brazilian Private Healthcare System is relatively high, mainly when there is progression to ESKD, reported by physicians in approximately 10% of LN patients.

The main factor contributing to the highest annual cost in patients with ESKD was undoubtedly the one related to dialysis, comprising 73.5% of the total cost observed. For LN classes III–IV, renal flares had a higher contribution, representing more than half (52.0%) of the total cost for this patient profile. For LN class V, analogous to ESKD, dialysis was the main cost driver, representing 36.3% of the total costs; renal flares contributed to more than one-third of the costs. Finally, the highest costs with refractory LN were immunosuppressant therapy, adjuvant therapy, and corticosteroid therapy, representing about half the cost in this category.

Dialysis was a significant factor in increasing the costs observed in this study. With a wide range of costs, starting from BRL 31,128.38 to BRL 239,490.15 per year, the current data highlight the importance of early SLE management to prolong the lifespan of the kidney and prevent or slow the progression to ESKD among LN patients. Dialysis is also the therapy of choice in cases of graft failure, a scenario in which patients with impaired renal function remain on dialysis until receiving a new transplant (Fiorentino et al., 2021). In Brazil, the average waiting time for a kidney transplant can reach 11 years (Marinho, 2006).

The use of higher-cost immunosuppressants, such as MMF, was an interesting finding in this study. For the Brazilian Private Healthcare System, it was reported that at least 40% of patients in all LN profiles were treated with MMF, suggesting access routes through the payment of treatment either by patients themselves or the liberality of some health operators through their protocols.

Clinical experience reported by the expert panel revealed a wide variety of immunosuppressants in use, which may reflect the difficulty in inducing response, maintaining it, or controlling episodes of renal flares. Data from the literature indicate that 1 in 4 patients with SLE with renal involvement does not effectively preserve the glomerular filtration rate in the long term (Anders et al., 2020, Klumb et al., 2021). It may be justified by the severity of the disease but also by other factors such as treatment interruptions, infections, and even low adherence to the treatment in Brazil (Klumb et al., 2021). According to national data, it is estimated that less than one-third of patients with SLE adhere to the correct use of the prescribed drugs. It is due to factors such as low rigor in following drug dosage, forgetfulness, adverse events related to treatment, and interruption by symptomatic improvement (Oliveira-Santos et al., 2011). These findings highlight an unmet need for new medications with more excellent response rates for patients with SLE.

Poor adherence to treatment may have impacted the observed high rate of renal flares reported by the expert panel, which was exceptionally high in classes III and IV with up to 4 episodes per year. This fact is supported by the literature, which indicates that non-adherence to immunosuppressive treatment in LN may increase the risk of renal flares by approximately five times (Ali et al., 2020). The current findings revealed that the renal flare cost per episode was BRL 15,060.10 for LN classes III and IV, BRL 10,040.07 for class V and BRL 8,366.72 for refractory LN. The observed differences in the total cost of renal flares among LN classes were driven by the percentage in which they occur and by the annual frequency reported by physicians, being higher and more frequent for LN classes III and IV, followed by class V and refractory LN. In general, the literature has limited data estimating the costs of a renal flare (Thompson et al., 2022). However, data from an international publication estimate that the costs of SLE flares, including renal activity flares, are USD 909 for mild flares, USD 1,539 for moderate flares, and up to USD 17,059 for severe flares (Garris *et al.*, 2013). More severe renal flares involve high doses of corticosteroids and greater use of medical and hospital resources, such as hospitalizations, consultations, and tests, causing a significant increase in cost (Garris *et al.*, 2013).

In addition, safety data in patients with frequent renal flares requiring higher dose of corticosteroids are scarce, and long-term studies on the adverse events of this approach are necessary. In addition to this associated cost, successive episodes of renal flares may compromise renal function and accelerate the progression to ESKD (Anders *et al.*, 2020). Although the occurrence of infections is not restricted to episodes of renal flare, conservatively and considering the difficulty in estimating the occurrence of infections during the follow-up of LN patients, only infections associated with renal flare were considered in this analysis.

The risk for patients using immunosuppressive therapy for transplant recipients was also identified in this study. A 20.0% rate for pneumonia infection was reported in patients receiving immunosuppressants either in the induction or maintenance period. According to a meta-analysis comprising 56 publications, of which 32 were randomized clinical studies, up to 22.8% of immunosuppressed patients with LN may develop pneumonia (Thong *et al.*, 2019).

The rate of transplanted patient rehospitalizations also draws attention, with an average of four new hospitalizations per year after renal transplantation, the first resulting from CMV in 80% of the cases. Although high, the literature reports a similar hospitalization rate of over 75% for new CMV infection or its reactivation after transplantation, applying not only to kidney transplantation but also to other solid organ transplants (Fishman *et al.*, 2007). Other disorders that may affect transplanted patients include nephropathy associated with polyomavirus, pneumonia (*Pneumocystis jirovecii*), and other potential community-acquired infections that are potentiated by the immunosuppression condition (Neuwirt, 2019).

Exploratorily, the percentages referring to each histological class or treatment profile of LN patients seen by the expert panel members were estimated. On average, it was reported that 48.1% of LN patients were classes III and IV, 21.4% were class V, 20.3% had refractory LN, and 10.3% had ESKD. According to a national study, it is estimated that about 56.6% are classes III and IV (including patients with characteristics in more than one histological class), 19.5% are of pure class V, and 10.2% are class VI, or ESKD, with no refractoriness condition reported, which demonstrates a certain similarity to the profiles observed in the current study (De Oliveira *et al.*, 2020).

Finally, it was found that the use of biopsies at different LN stages, reflecting the most current recommendations of international guidelines for LN, remains the gold standard. Specialists perform it according to these recommendations in 76.0% of patients at diagnosis, 12.5% for determining refractory LN, and 6.0% in case of renal flares. It is also known that there are still several barriers to broad access to repeat biopsies in Brazil, such as the relatively low availability of services specialized in pathology, invasive nature, and associated complications, as well as the high procedure cost (Klumb *et al.*, 2021). The low availability may not only delay the initiation of the therapy but also lead to suboptimal use of the therapeutic strategy, compromising patient outcomes (Klumb *et al.*, 2021). An example of this importance is the fact that there is a 40–76% probability of histological changes (typically from LN class V to classes III-IV) after a renal flare (Fanouriakis *et al.*, 2020). Such conditions present a higher risk of irreversible nephron damage, which should be quickly managed (Sprangers *et al.*, 2012). In a scenario where only 6% of patients after a renal flare could be identified for this transition, the outcomes of LN patients are questioned.

This study has some limitations. One limitation is the descriptive nature of the clinical experience of physicians who made up the expert panel, whose LN patients can be quite heterogeneous, affecting how management is reported. The dependence on estimates for the use of resources captured in the study is also a significant limitation and may underestimate or overestimate some of the reported values (Bertens *et al.*, 2013). Another limitation concerns the nature of the study conducted; in a panel of experts, a dominant view may have an influence on physicians' response (European Union (EU), 2017). However, mitigation of this limitation was sought by implementing a previous questionnaire with individual responses.

Moreover, the opinion of the interviewed physicians may not represent the general opinion of all specialists in the country, considering the number of participating physicians and even regional differences. It should also be noted that although the National Institute of Health recommends six months for induction treatment, the EULAR recommendations were used in this study for the drug defrayal phase. It suggests only three months of induction, in line with provisions of the Brazilian Consensus of Lupus Nephritis of 2015, which provides for two possibilities, 3 or 6 months of induction.

Finally, adverse events arising from immunosuppression or corticosteroid therapy were not considered in the defrayal of LN patients and may underestimate the economic impact in this profile of patients. The clinical guidelines for LN converge in the sense that when a response is reached after the induction period, the immunosuppression and corticosteroid therapy regimen should be changed in the maintenance period to minimize the risks to the patient, given the prolonged exposure to these agents (Fanouriakis *et al.*, 2020, Klumb *et al.*, 2015).

According to EULAR recommendations from 2019, after a response is reached in the induction period, the recommended immunosuppressants during maintenance are MMF, AZA, and CsA, since these agents can reduce the use of glucocorticoids; corticosteroid therapy should be reduced to 7.5 mg per day, in an equivalent dose of prednisone, or even discontinued, due to the risk of irreversible damage to different organs of LN patients (Fanouriakis *et al.*, 2020).

Considering the socioeconomic disparities in the country, the diagnosis of one of the most severe complications of SLE, LN, remains a challenge in the early identification of patients and fast institution of therapy, which allow the achievement of better results in the control of the disease and the prevention of progressive and irreversible damage to the kidneys (Furie *et al*., 2020). Another challenge is anchored in measures that allow improved adherence to treatment, a fundamental point to mitigate the consequences of the lack of LN control.

## Conclusions

The panel of experts indicated a significant cost increase as LN patients develop the most severe forms of the disease, particularly in the face of progression to ESKD. In these disease stages, the highest costs are associated with dialysis, kidney transplantation, and management of renal flares, critical aspects for the Brazilian Private Healthcare System. The system bears these treatments directly or indirectly through reimbursements, which can be mitigated if these patients are treated early.

Considering this is a younger working-age population with a long-term horizon, the prioritization of essential elements for the prevention of additional costs is highly relevant, allowing greater chances for improved management, outcomes with better quality of life, and implementation of standardized treatment approaches that can optimize resource management and costs in the healthcare system.

## Acknowledgments

Editorial support (in the form of copy editing and collating author comments) was provided by Robert Bloxham, Ph.D., Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK. Technical revision was provided by authors AH and OM.

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**Supplementary Table 1.** Use of resources and weighted cost related to dialysis in patients with graft failure (5% of kidney transplants) over the course of 1 year

| Graft failure management | Frequency | Number of sessions | Weighted cost |
|---|---|---|---|
| Hemodialysis | 90.0% | 150 | BRL 11,356.04 |
| Peritoneal dialysis | 10.0% | 350 | BRL 4,437.63 |
| Weighted annual cost | | | BRL 15,793.67 |

**Supplementary Table 2.** Use of resources and weighted cost related to renal pre-transplant examinations

| Tests, consultations, or procedures | Frequency | Weighted Cost |
|---|---|---|
| Consultation with specialist | 100.0% | BRL 224.90 |
| Anti-nuclear factor | 33.3% | BRL 8.86 |
| Native or double helix anti-DNA autoantibodies (dsDNA) | 50.0% | BRL 15.96 |
| Serum complement dosage (C3) | 50.0% | BRL 15.59 |
| Serum complement dosage (C4) | 50.0% | BRL 15.59 |
| Isolated samples of urinalysis | 33.3% | BRL 3.61 |
| 24-hour urinalysis | 50.0% | BRL 20.53 |
| Serum albumin | 33.3% | BRL 2.91 |
| Chest X-ray | 33.3% | BRL 41.92 |
| Creatinine clearance | 33.3% | BRL 8.01 |
| HBsAg | 33.3% | BRL 19.30 |
| Anti-HCV | 33.3% | BRL 18.45 |
| Anti-HIV | 33.3% | BRL 37.03 |
| IgG cytomegalovirus, dosage | 33.3% | BRL 13.22 |
| IgM cytomegalovirus, dosage | 33.3% | BRL 16.04 |
| Cross matching with HLA A, B, C and D/DR genotyping of donor and recipient | 66.7% | BRL 631.60 |
| Microscopic examination of urine sediment | 33.3% | BRL 6.24 |
| Urinary protein/creatinine ratio | 16.7% | BRL 4.45 |
| Sodium | 33.3% | BRL 2.91 |
| Potassium | 33.3% | BRL 2.91 |
| Coagulogram | 33.3% | BRL 18.21 |
| Chest CT | 33.3% | BRL 353.95 |
| Abdominal CT | 33.3% | BRL 508.13 |
| **Total weighted cost** | | **BRL 1,990.28** |

CT: computed tomography; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; Ig: immunoglobulin.

**Supplementary Table 3.** Use of resources and weighted cost related to tests and procedures for kidney transplantation from deceased donors (90% of patients; adapted from Silva et el. 2016)

| Tests, consultations, or procedures | Frequency | Weighted cost |
|---|---|---|
| **Examinations and procedures for inclusion on the organ waiting list** | | |
| Chlorine | 100.0% | BRL 7.85 |
| Cholesterol (HDL) | 100.0% | BRL 10.85 |
| Cholesterol (LDL) | 100.0% | BRL 14.40 |
| Cholesterol (VLDL) | 100.0% | BRL 14.40 |
| Total acid phosphatase | 100.0% | BRL 14.40 |
| Total protein albumin and globulin | 100.0% | BRL 10.85 |
| Magnesium | 100.0% | BRL 7.85 |
| Sodium | 100.0% | BRL 7.85 |
| Potassium | 100.0% | BRL 7.85 |
| Glucose | 100.0% | BRL 7.85 |
| Creatinine, dosage | 100.0% | BRL 7.85 |
| Liver function | 100.0% | BRL 101.31 |
| Blood gas + Hb + Ht + Na + K + Cl + Ca + glucose + lactate | 100.0% | BRL 11.52 |
| Complete blood count | 100.0% | BRL 17.36 |
| Prothrombin time, determination | 100.0% | BRL 11.39 |
| Coagulogram | 100.0% | BRL 49.16 |
| Free prostate-specific antigen (PSA free) | 100.0% | BRL 63.14 |
| Isolated sample of urinalysis | 100.0% | BRL 9.75 |
| Creatinine clearance | 100.0% | BRL 21.62 |
| Fresh, examination | 100.0% | BRL 14.53 |
| Stools parasitological analysis | 100.0% | BRL 19.14 |
| ABO and RH blood group | 100.0% | BRL 26.01 |
| Anti-HIV | 100.0% | BRL 99.99 |
| HTLV1 or HTLV2 antibody search (each) | 100.0% | BRL 81.98 |
| HBsAg | 100.0% | BRL 52.10 |
| S. Hepatitis B anti-HBC by hemotherapy component | 100.0% | BRL 28.99 |
| S. Hepatitis C anti-HCV by hemotherapy component | 100.0% | BRL 62.68 |
| Hepatitis B – HBSAC (surface anti-antigen), search and/or dosage | 100.0% | BRL 36.34 |
| Anti-HCV | 100.0% | BRL 49.82 |
| Chagas IgG, dosage | 100.0% | BRL 36.34 |
| Chagas IgM, dosage | 100.0% | BRL 43.97 |
| Cytomegalovirus IgG, dosage | 100.0% | BRL 35.69 |
| Cytomegalovirus IgM, dosage | 100.0% | BRL 43.31 |
| Toxoplasmosis IgG, dosage | 100.0% | BRL 43.31 |
| Toxoplasmosis IgG, dosage | 100.0% | BRL 43.31 |
| S. syphilis VDRL by hemotherapy component | 100.0% | BRL 6.53 |
| Syphilis – VDRL | 100.0% | BRL 15.07 |
| 6-minute walk test | 100.0% | BRL 291.71 |
| Alpha-fetoprotein, dosage | 100.0% | BRL 56.91 |
| Mononucleosis, anti-VCA (EBV) IgG, search and/or dosage | 100.0% | BRL 43.97 |
| Mononucleosis, anti-VCA (EBV) IgM, search and/or dosage | 100.0% | BRL 49.82 |

| Tests, consultations, or procedures | Frequency | Weighted cost |
|---|---|---|
| Adult uretrocistography | 100.0% | BRL 356.33 |
| Transthoracic echocardiography with bidimensional STRAIN (includes transthoracic) | 100.0% | BRL 709.37 |
| X-Ray– chest – 2 incidences | 100.0% | BRL 83.84 |
| US – Total abdomen (upper abdomen, kidneys, bladder, aorta, inferior and adrenal vena cava) | 100.0% | BRL 510.61 |
| Urinary tract ultrasound | 100.0% | BRL 276.88 |
| Upper digestive endoscopy | 100.0% | BRL 1,001.50 |
| Cardiac catheterization D and/or E with or without cinecoronariography / cineangiography with evaluation of pulmonary vascular reactivity or homodynamic overload test | 100.0% | BRL 2,186.39 |
| Complete urodynamics | 100.0% | BRL 1,081.99 |
| **Intensive care unit daily stay of probable organ donor** | **100.0%** | **BRL 666.00** |
| **Uni/bilateral kidney withdrawal (for transplantation)** | **100.0%** | **BRL 3,261.01** |
| **Kidney transplant** | **100.0%** | **BRL 4,335.62** |
| **Days of hospitalization for transplant procedure** | **100.0%** | **BRL 2,710.76** |
| **Clinical follow-up of renal transplantation during hospitalization (post-operative up to 15 days)** | **100.0%** | **BRL 4,335.62** |
| **Total weighted cost** | | **BRL 23,094.63** |

EBV: Epstein-Barr virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HDL: high-density lipoprotein; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; HTLV-1/2: human T-lymphotropic virus type 1/2; Ig: immunoglobulin; LDL: low-density lipoprotein; US: ultrasound; VCA: viral capsid antigen; VDRL: Venereal Disease Research Laboratory test; VLDL: very-low-density lipoprotein.

**Supplementary Table 4.** Use of resources and weighted cost related to tests and procedures for kidney transplantation from living donor (10% of patients)

| Tests, consultations, or procedures | Frequency | Weighted cost |
|---|---|---|
| **Examinations for clinical investigation in the living kidney donor** | | |
| Uric acid, dosage | 100.0% | BRL 0.87 |
| Bilirubin (direct, indirect, and total), dosage | 100.0% | BRL 0.87 |
| Chlorine | 100.0% | BRL 0.87 |
| Cholesterol (HDL) | 100.0% | BRL 1.21 |
| Cholesterol (LDL) | 100.0% | BRL 1.60 |
| Cholesterol (VLDL) | 100.0% | BRL 1.60 |
| Total acid phosphatase | 100.0% | BRL 1.60 |
| Total proteins albumin and globulin | 100.0% | BRL 1.21 |
| Magnesium | 100.0% | BRL 0.87 |
| Sodium | 100.0% | BRL 0.87 |
| Potassium | 100.0% | BRL 0.87 |
| Glucose | 100.0% | BRL 0.87 |
| Creatinine, dosage | 100.0% | BRL 0.87 |
| Liver function | 100.0% | BRL 11.26 |
| Complete blood count | 100.0% | BRL 1.93 |
| Prothrombin time, determination | 100.0% | BRL 1.27 |
| Coagulogram | 100.0% | BRL 5.46 |
| Hemosedimentation, (VHS), speed | 100.0% | BRL 0.87 |
| Urine culture | 100.0% | BRL 4.04 |
| Microscopic examination of urine sediment | 100.0% | BRL 1.87 |
| Creatinine clearance | 100.0% | BRL 2.40 |
| ABO and RH blood group | 100.0% | BRL 2.89 |

| Tests, consultations, or procedures | Frequency | Weighted cost |
|---|---|---|
| US –total abdomen (upper abdomen, kidneys, bladder, aorta, inferior and adrenal vena cava) | 100.0% | BRL 56.73 |
| Plain abdominal X-ray | 100.0% | BRL 9.40 |
| Ergometer exercise test with electrocardiogram monitoring | 100.0% | BRL 16.35 |
| X-Ray – chest – 2 incidences | 100.0% | BRL 9.32 |
| Transthoracic echocardiography with bidimensional STRAIN (includes transthoracic) | 100.0% | BRL 78.82 |
| Abdominal CT | 100.0% | BRL 152.44 |
| Pelvis arterial angio-MRI | 100.0% | BRL 173.87 |
| Venous urography with nephrotomography | 100.0% | BRL 41.41 |
| **Uni/bilateral kidney withdrawal (for transplantation)** | **100.0%** | **BRL 362.33** |
| **Kidney transplant** | **100.0%** | **BRL 481.74** |
| **Days of hospitalization for transplant procedure** | **100.0%** | **BRL 301.20** |
| **Clinical follow-up of renal transplantation during hospitalization (post-operative up to 15 days)** | **100.0%** | **BRL 481.74** |
| **Total weighted cost** | | **BRL 2,211.52** |

CT: computed tomography; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MRI: magnetic resonance imaging; US: ultrasound; VHS: velocity of hemosedimentation; VLDL: very-low-density lipoprotein.

**Supplementary Table 5.** Use of resources and weighted cost related to the management of post-transplant infections over the course of 1 year

| Management of post-transplant infections | Frequency | Weighted cost |
|---|---|---|
| **Cytomegalovirus – 80% of transplanted patients** | | |
| Outpatient consultation | 100.0% | BRL 245.29 |
| Cytomegalovirus IgG, dosage | 100.0% | BRL 31.72 |
| Cytomegalovirus IgM, dosage | 100.0% | BRL 38.50 |
| Hospitalizations | 100.0% | BRL 3,614.86 |
| Ganciclovir | 100.0% | BRL 5,449.25 |
| **Other causes – 20% of transplanted patients** | | |
| Hospitalizations | 100.0% | BRL 2,711.14 |
| Emergency visits | 35.0% | BRL 60.20 |
| **Weighted annual cost** | | **BRL 12,150.95** |

Ig: immunoglobulin.

**Supplementary Table 6.** Use of resources and weighted cost related to follow-up and immunosuppression of transplanted patients over the course of 1 year

| Consultation or medicine | Frequency | Number of packs | Weighted cost |
|---|---|---|---|
| Consultation with specialist | 98.0% | - | BRL 440.80 |
| Tacrolimus | 75.0% | 91 | BRL 14,365.94 |
| Mycophenolate mofetil | 45.0% | 144 | BRL 8,892.50 |
| Azathioprine | 3.8% | 23 | BRL 88.41 |
| Sirolimus | 1.3% | 31 | BRL 925.90 |
| **Weighted annual cost** | | | **BRL 24,713.55** |