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# Oral shedding of HSV-1 and EBV and oral manifestations in paediatric chronic kidney disease patients and renal transplant recipients

Rubens Caliento[a], Dmitry José de Santana Sarmento[a], Érika Mont'alverne Pereira Silva[a], Tânia Regina Tozetto-Mendoza[b], Priscila Lie Tobouti[a], Vanda Benini[c], Paulo Henrique Braz-Silva[b,d] and Marina Gallottini[a]

[a]Department of Stomatology, Division of Oral Pathology, School of Dentistry, University of São Paulo, São Paulo, Brazil; [b]Laboratory of Virology, Institute of Tropical Medicine, University of São Paulo, São Paulo, Brazil; [c]Department of Nephrology, School of Medicine, Irmandade Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil; [d]Department of Stomatology, Division of General Pathology, School of Dentistry, University of São Paulo, São Paulo, Brazil

**ABSTRACT**

**Objective:** Previous research demonstrated that salivary shedding of HSV-1 and EBV occurs often in adult renal transplant recipients, but there is a lack of studies on the presence of them in the saliva of paediatric population. Therefore, the objective of this study is to describe oral characteristics and to compare the shedding profile of HSV-1 and EBV in the saliva of children with renal transplant to that of chronic kidney disease patients and controls.

**Methods:** This is a cross-sectional study involving 100 children, being 25 renal transplant recipients, 25 chronic kidney disease patients and 50 healthy children. Demographic and oral clinical characteristics were assessed. Saliva samples were collected and submitted to screening for EBV and HSV-1 by using nested polymerase chain reaction technique. Fisher's exact, Pearson's chi-square and Kruskal–Wallis tests were used for statistical analysis at a significance level of 5%.

**Results:** Oral shedding of HSV-1 (28%) and EBV (60%) were significantly higher in renal transplant recipients compared to the other groups. Single vesicles in the oral mucosa were statistically associated with the presence of HSV-1 ($p = .035$). In children with chronic kidney disease, there was a higher prevalence of pale oral mucosa (32%) and enamel hypoplasia (40%) compared to paediatric renal transplant recipients and controls. Dental calculus (36%), candidiasis (8%), drug-induced gingival overgrowth (16%), mouth blisters (8%), xerostomia (12%) and salivary gland enlargement (20%) were more common in paediatric renal transplant recipients.

**Conclusions:** Therefore, it can be concluded that salivary shedding of HSV-1 and EBV in paediatric patients was more often found in renal transplant recipients than in the renal failure and control children. Transplanted recipients showed more oral manifestations than renal failure and control children did.

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Kidney transplantation; chronic kidney disease; oral shedding; human herpesviruses; paediatrics

## Introduction

Chronic kidney disease has emerged as a serious public health problem, but is relatively uncommon in children. The main aetiological factors of chronic kidney disease in children are represented by congenital abnormalities of the kidney and urinary tract [1]. Some common aspects, such as glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis are present in chronic kidney disease and eventually, irreversible changes and nephron destruction can occur, leading to end-stage kidney disease [1,2].

Paediatric renal transplant remains the treatment of choice for patients with end-stage chronic renal disease and kidney failure [3]. In Brazil, there is a record of 310 paediatric renal transplantations *per* year, which represents 58.9% of all paediatric solid organ transplants (527 *per* year). This therapeutic option requires long-term immunosuppressive therapy in order to reduce rejection rate and increase graft survival [4].

Induction therapy, maintenance therapy and treatment of acute rejection can be applied in children who undergo renal transplantation, with the choices of medication depending on the transplantation centre. Immunosuppressive protocols have improved remarkably and brought successful results in renal transplantation, although many immunosuppressive drugs (e.g. corticosteroids, anti-metabolic agents and calcineurin inhibitors) have paediatric side effects, such as toxicity and increased susceptibility to serious infections, which consequently contributes to graft rejection [5].

Two common opportunistic viruses found in the oral cavity are herpes simplex virus, type 1 (HSV-1) [6], and Epstein–Barr virus (EBV). Studies suggest that HSV-1 and EBV are the most common infectious agents as they are present in 70% of the paediatric population [7–12].

HSV-1 infection often occurs during the early stage of life and can remain latent in the trigeminal ganglion, thus 90% of the normal asymptomatic individuals are seropositive.

CONTACT Paulo Henrique Braz-Silva pbraz@usp.br Department of Stomatology, Division of General Pathology, University of São Paulo, Avenida Professor Lineu Prestes, 2227 Cidade Universitária, São Paulo, SP, Brazil

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However, the virus can be triggered and reactivated by many environmental factors, such as ultraviolet light, social stress and medications, leading to disease progression [13]. In general, reactivation occurs in the first weeks after transplantation [14] and can produce bullous-vesicular lesions, organ infections, encephalitis, pneumonia, visceral dissemination and even hepatitis, which can be life-threatening to the patient [12].

EBV infection is important in renal transplantation due to its high prevalence, wide variety of associated diseases, immune-modulatory capacity of the virus and high rate of morbidity and mortality [15]. The consequences of the presence of EBV to transplanted children range from mild symptoms to severe illness, such as post-transplant lymphoproliferative diseases [16].

Although previous publications on the shedding profile of human herpesviruses in saliva of adult renal transplant recipients have been published by our group [17], there is a lack of studies describing the presence of HSV-1 and EBV in the saliva of paediatric renal transplant and chronic kidney disease patients. Therefore, the objective of this study is to describe the oral characteristics and to compare the shedding profile of HSV-1 and EBV in the saliva of children with renal transplant to those of chronic kidney disease and control groups.

## Materials and methods

This study was approved by the Institutional Review Board of the Dental School of the University of São Paulo. Each child's legal guardian authorized their participation in the study by signing an informed consent form. All the procedures involving human participants were performed in accordance with the institution's and/or national research committee's ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### *Subjects and sample collection*

A cross-sectional study was conducted based on a convenience selection of 100 paediatric individuals divided into three groups: (a) chronic kidney disease group, with 25 children; (b) Renal transplant recipient group, with 25 (18 individuals transplanted for more than 6 months and 7 for less than 6 months); and (c) Control group, with 50 clinically healthy children (i.e. no history of renal disease) who were attending the paediatric dental clinic. These participants were recruited from the Nephrology Clinic of the Holy House of Mercy Hospital. All children were between 0 and 15 years old.

Demographic and clinical characteristics of the patients were assessed through interview and physical exam. Oral health was characterized based on modified gingival index [9], visible dental plaque [10], drug-induced gingival overgrowth [11], and decayed, missing and filled teeth index. An appropriately qualified and trained investigator assessed these indices and the records were registered on a special form designed for this study. Other variables analysed were dental calculus, paleness of oral mucosa, candidiasis, enamel hypoplasia, oral blisters, xerostomia and salivary gland enlargement.

EBV and HSV-1 were detected in saliva by using the polymerase chain reaction technique. The subjects were instructed to not eat or drink for at least 20 min prior to the saliva collection. Each patient received a foam collector with capacity to collect 1 ml of saliva (Salivette oral test kit, Sarstedt Ltd., Rio de Janeiro, Brazil). The patient was instructed to maintain the foam inside the mouth for 2 min, after which the collectors were placed in appropriate tube and stored at −20 °C.

### *DNA isolation and nested polymerase chain reaction*

Total DNA was isolated by using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Primer sequences were based on previously published primers [18] as follows: HSV-1, First round, forward: 5′-TACATCGGCGTCATCTACGGGG-3′; reverse: 5′ -GGG CCAGGCGCTTGTTGGTGTA-3′. Second round, forward: 5′ -GCG TTTATCAACCGCACCTCC-3′; reverse 5′ -CAGTTCGGCGGTGAGG ACAAA-3′. EBV, First round, forward: 5′ - AGGGATGCCTGG ACACAAGA-3′; reverse: 5′ -TGTGCTGGTGCTGCTGGTGG-3′. Second round, 5′ -AACTTCAACCCACACCATCA-3′; reverse: 5′-TTCTGGACTATCTGGATCAT-3′.

Nested polymerase chain reaction was carried out in triplicate for detection of HSV-1 and EBV [18,19] in a final volume of 25 uL (200 mM Tris–HCl, pH 8.4, 500 mM KCl, 0.3 mM dNTP, $MgCl_2$ and primers). Experiments were run in triplicate and the cycling conditions as follows: initially, one cycle at 95 °C/3 min, 35 cycles at 94 °C/1 min and one cycle at 65 °C/1 min, 72 °C/1 min and 72 °C/7 min; nested reaction, one cycle at 95 °C/3 min, followed by 30 cycles at 94 °C/1 min and one cycle at 55 °C/1 min, 72 °C/1 min and 72 °C/7 min. The results were analysed by electrophoresis in 2% agarose gel containing 0.5 ug/mL of ethidium bromide and visualized under ultraviolet light.

### *Statistical analysis*

Statistical tests were performed by using the Statistical Package for Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, IL). To compare the presence of oral alterations between all the groups evaluated, as well as the presence of HSV-1 and EBV, we have used Pearson's chi-squared test. To compare the visible dental plaque, modified gingival index, and decayed, missing and filled teeth indices between all the groups, Kruskal–Wallis test was used. Fisher's exact test was applied to compare the presence of blisters in patients positive for EBV and HSV-1. The significance level of 5% ($p < .05$) was adopted in all statistical tests.

## Results

### *Demographic and clinical presentation*

The clinical characteristics are summarized in Table 1. Patients with chronic kidney disease were mostly black

females with mean age of 9.26 ± 4.01 years (range 1–15 years), and glomerulonephritis was the main underlying associated disease. Patients with paediatric renal transplant were mainly white males with mean age of 8.48 ± 3.58 years (range 1–14 years) and the primary disorders leading to renal transplant were nephrotic syndrome (40%), glomerulonephritis (28%), bilateral renal hyperplasia (16%) and focal segmental glomerulosclerosis (8%), followed by bilateral polycystic kidney disease and hypertension (both affecting 4%). Subjects in the control group were in the majority white males with mean age of 8.52 ± 2.5 years (range 4–15).

### *Oral manifestations*

Patients with chronic kidney disease presented a higher prevalence of pale oral mucosa and enamel hypoplasia compared to that of renal transplant recipients and controls. Dental calculus, candidiasis, drug-induced gingival overgrowth, mouth blisters, xerostomia and salivary gland enlargement were more common in renal transplant recipients. All these results were statistically significant (Table 2). Three out of the four patients with xerostomia were hypertensive and a statistical association between these variables was noticed ($p = .032$, Fisher's exact test).

Quantitative assessment of the variables visible dental plaque-modified gingival index, and decayed, missing and filled teeth index did not demonstrate any statistical differences in the comparison between the groups, with mean values being similar between them (Table 3).

### *Incidence of HSV-1 and EBV in the saliva*

The majority of the samples with salivary shedding of HSV-1 and EBV was found in renal transplant recipients, individually or in co-infection, compared to control and chronic kidney patients. The results showed statistical significance for salivary excretion of EBV individually and in association with HSV-1 (Figure 1).

Individuals with vesicles in the oral cavity were from the renal transplant group, and a statistical association between this lesion and HSV-1, alone or concomitant with EBV was observed (Table 4).

**Table 1.** Characterization of the participants according to gender, ethnicity and underlying disease.

| | Control | | Chronic kidney disease patients | | Renal transplant recipients | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Gender | | | | | | |
| Male | 28 | 56.0 | 11 | 44.0 | 13 | 52.0 |
| Female | 22 | 44.0 | 14 | 56.0 | 12 | 48.0 |
| Total | 50 | 100.0 | 25 | 100.0 | 25 | 100.0 |
| Ethnicity | | | | | | |
| Black race | 8 | 16.0 | 10 | 40.0 | 6 | 24.0 |
| Caucasian | 35 | 70.0 | 8 | 32.0 | 12 | 48.0 |
| Mulatto | 7 | 14.0 | 7 | 28.0 | 7 | 28.0 |
| Total | 50 | 100.0 | 25 | 100.0 | 25 | 100.0 |
| Base disease | | | | | | |
| Nephrotic syndrome | – | – | 7 | 28.0 | 10 | 40.0 |
| Focal segmental glomerulosclerosis | – | – | 0 | 0 | 2 | 8.0 |
| Bilateral polycystic kidney | – | – | 1 | 4.0 | 1 | 4.0 |
| Bilateral renal hyperplasia | – | – | 3 | 12.0 | 4 | 16.0 |
| Glomerulonephritis | – | – | 10 | 40.0 | 7 | 28.0 |
| Hypertension | – | – | 0 | 0 | 1 | 4.0 |
| Uremic bladder | – | – | 1 | 4.0 | 0 | 0 |
| Haemolytic uremic syndrome | – | – | 1 | 4.0 | 0 | 0 |
| Multiple | – | – | 2 | 8.0 | 0 | 0 |
| Total | 50 | 100.0 | 25 | 100.0 | 25 | 100.0 |

## Discussion

In this study, we have compared the occurrence of HSV-1 and EBV in the saliva and described the oral health profile between these patients. To the best of our knowledge, there is no work comparing these two important viruses in three different paediatric groups (i.e. chronic kidney disease patients, renal transplant recipients and controls) regarding the description of their oral health profile.

Similar approaches and maintenance of immunosuppressive medication are used for both children and adults [20]. However, children require longer immunosuppressive therapy after transplantation as acute and long-term adverse effects are a challenge [16]. The level of immunosuppression influences the infectious conditions and is linked to the immunotherapy used. In general, 90% of the infections occur during the first six months after transplantation due to induction therapy and peak of immunosuppression [4,5,21], in which clinical manifestations resulting from opportunistic microorganisms can be seen in any topographic area of the patient's body, including oral cavity [22].

Despite the great advances in kidney transplantation, human herpesvirus infection is still a major concern. The immune system plays a key role in the clearance of viral particles, but this herpesvirus can remain latent for many years and be reactivated late in life, resulting in recurrent infection and associated diseases [23]. We have demonstrated a higher presence of HSV-1 and EBV in the saliva of paediatric renal transplant patients compared to chronic kidney disease and normoreactive children. As children with renal transplant were immunosuppressed, this finding was already expected and is in accordance with other works [14,15,24]. The main goal of viral surveillance, such as investigation of HSV-1 and EBV, is to predict possible complications that may occur and to detect subclinical viral infections in order to prevent disease progression or enable early diagnosis of viral disease [25]. Both HSV-1 and EBV can be found in epithelial cells of the buccal mucosa as well in saliva, thus serving as a non-invasive tool for viral diagnosis [26,27].

EBV, human herpesvirus 4, a gamma herpes virus, is excreted in saliva and spread by close contact [14]. In general, exchange of oral secretions through sharing of objects is the main pathway by which children are infected [28]. However, children can acquire primary EBV after transplantation in which the donor's organ is infected or through contaminated blood transfusion [24]. Prospective surveillance studies show that subclinical EBV infection occurs in 35–40% of the paediatric kidney transplant recipients [25]. A major concern is the post-transplant lymphoproliferative disorder, which is strongly associated with EBV and mortality in solid

**Table 2.** Oral manifestation observed in the participants.

| | Groups | | | |
|---|---|---|---|---|
| | Control *n* (%) | Chronic kidney disease patients *n* (%) | Renal transplant recipients *n* (%) | *p*[a] |
| Caries | | | | |
| Yes | 17 (34.0) | 2 (8.0) | 2 (8.0) | .006* |
| No | 33 (66.0) | 23 (92.0) | 23 (92.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Dental calculus | | | | |
| Yes | 3 (6.0) | 6 (24.0) | 9 (36.0) | .004* |
| No | 47 (94.0) | 19 (76.0) | 16 (64.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Pale oral mucosa | | | | |
| Yes | 0 (0.0) | 8 (32.0) | 0 (0.0) | <.001* |
| No | 50 (0.0) | 17 (68.0) | 25 (100.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Candidiasis | | | | |
| Yes | 0 (0.0) | 0 (0.0) | 2 (8.0) | .047* |
| No | 50 (100.0) | 25 (100.0) | 23 (92.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Enamel hypoplasia | | | | |
| Yes | 6 (12.0) | 10 (40.0) | 9 (36.0) | .010* |
| No | 44 (88.0) | 15 (60.0) | 16 (64.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Drug-induced gingival overgrow | | | | |
| Yes | 0 (0.0) | 0 (0.0) | 4 (16.0) | .002* |
| No | 50 (100.0) | 25 (100.0) | 21 (84.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Blisters | | | | |
| Yes | 0 (0.0) | 0 (0.0) | 2 (8.0) | .047* |
| No | 50 (100.0) | 25 (100.0) | 23 (92.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Xerostomia | | | | |
| Yes | 0 (0.0) | 1 (4.0) | 3 (12.0) | .044* |
| No | 50 (100.0) | 24 (96.0) | 22 (88.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |
| Salivary gland enlargement | | | | |
| Yes | 0 (0.0) | 2 (8.0) | 5 (20.0) | .006* |
| No | 50 (100.0) | 23 (92.0) | 20 (80.0) | |
| Total | 50 (100.0) | 25 (100.0) | 25 (100.0) | |

[a]Pearson's chi-squared test.
*Results are statistically significant ($p < .05$).

**Table 3.** Comparison of visible plaque index, gingival index and decayed, missed and filled teeth index among chronic kidney disease patients, renal transplant recipients and controls.

| | *n* | Mean ± SD | Median | $Q_{25}$–$Q_{75}$ | Mean of ranks | *p*[a] |
|---|---|---|---|---|---|---|
| Visible dental plaque | | | | | | |
| Control | 50 | 5.64 ± 11.97 | 0 | 0–5 | 48.30 | .448 |
| Chronic kidney disease patients | 25 | 3.44 ± 4.77 | 2 | 0–6 | 55.90 | |
| Renal transplant recipients | 25 | 2.82 ± 4.93 | 0 | 0–5 | 49.50 | |
| Modified gingival index | | | | | | |
| Control | 50 | 2.64 ± 5.40 | 0 | 0–3.25 | 47.50 | .246 |
| Chronic kidney disease patients | 25 | 3.80 ± 6.02 | 1 | 0–4.5 | 57.60 | |
| Renal transplant recipients | 25 | 2.12 ± 5.01 | 0 | 0–3.5 | 49.40 | |
| Decayed, missed and filled teeth index | | | | | | |
| Control | 50 | 1.92 ± 2.56 | 0 | 0–4 | 52.27 | .511 |
| Chronic kidney disease patients | 25 | 1.04 ± 1.42 | 0 | 0–2 | 45.12 | |
| Renal transplant recipients | 25 | 1.76 ± 2.24 | 1 | 0–3.5 | 52.34 | |

SD: standard deviation
[a]Kruskal–Wallis test.

organ transplantations, accounting for 50–70% of the cases [29].

HSV-1, an alpha herpes virus, causes the classic herpes labials lesions. This virus is usually acquired early in life and the lack of homeostasis can lead to pathologies. Only a few immunocompromised patients will develop disease, but many will shed the virus in the mucosa [30] and saliva [26]. HSV-1 has also been shown to reactivate latent EBV (i.e. lytic replication cycles) [31] and to facilitate EBV infection, which could result in more infected lymphocytes, worse oral lesions and induce oncogenic alterations. This finding is important because we have found an association between EBV and HSV-1 in the renal transplant recipients, including oral blisters associated with their presence.

Oral health is an important component of the overall health status in immune-deficient patients. Besides the common infections of EBV and HSV-1, we have found that oral manifestations, such as dental calculus, candidiasis, mouth

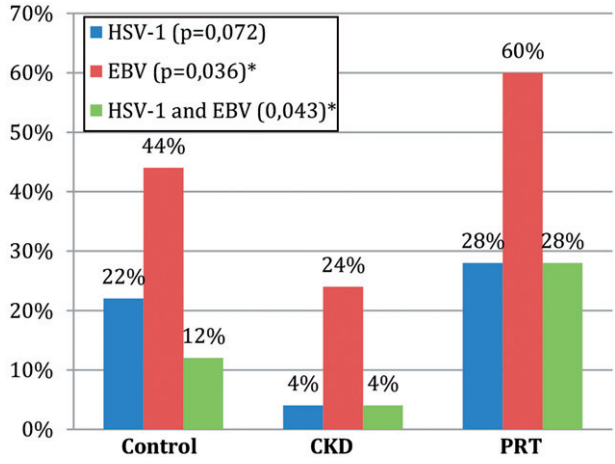


**Figure 1.** Oral shedding of HSV-1 and EBV in the three groups studied. *$p < .05$, Pearson's chi-squared test.

**Table 4.** Relation of salivary excretion to EBV and HIV-1 and presence of vesicles in the oral cavity in all participants.

| | Blisters | | |
|---|---|---|---|
| | Yes *n* (%) | No *n* (%) | *p*[a] |
| EBV | | | |
| Yes | 2 (100.0) | 41 (41.8) | .182 |
| No | 0 (0.0) | 57 (58.2) | |
| Total | 2 (100.0) | 98 (100.0) | |
| HSV-1 | | | |
| Yes | 2 (100.0) | 17 (17.3) | .035* |
| No | 0 (0.0) | 81 (82.7) | |
| Total | 2 (100.0) | 98 (100.0) | |
| EBV and HSV-1 | | | |
| Yes | 2 (100.0) | 12 (12.2) | .018* |
| No | 0 (0.0) | 86 (87.8) | |
| Total | 2 (100.0) | 98 (100.0) | |

[a]Fisher's exact test.
*Results are statistically significant.

blisters, drug-induced gingival overgrowth, salivary gland enlargement and xerostomia were more present in renal transplant recipients. These oral manifestations are commonly seen in transplanted immunocompromised patients, which is in accordance with previous studies on adults [32–34] and children [35]. Immunosuppressive drugs, corticosteroids and antimicrobial agents contribute to the cause of the majority of these lesions, thus reducing both immune system activation and salivary secretion rate. This, in turn, results in a shift towards the ability to inhibit cariogenic microorganisms [32], but which also potentiates opportunist fungi, such as Candida [36], and disrupts collagen synthesis and degradation by lowering phagocytosis and inducing gingival fibroblasts [32,37]. Paediatric patients with chronic kidney disease also exhibit oral alterations, such as pale oral mucosa and enamel hypoplasia. Patients undergoing haemodialysis can present pale mucosa resulting from the inability of the kidney to secrete erythropoietin and a low count of red blood cells [38]. Children who suffer from chronic kidney disease have a high risk of developing altered tooth enamel, which is probably associated with changes in calcium and phosphorus metabolism. This can trigger an alteration called enamel hypoplasia, in which there is an increase in the porosity of the dental surface [39].

Interestingly, our results have shown a similar quantitative assessment of visible dental plaque, modified gingival, and decayed, missing and filled teeth indices in all groups as all the subjects presented poor oral hygiene, gingivitis and a moderate incidence of cavities. Cavities and periodontal diseases have a multifactor aetiology and from our data records, we were unable to understand why there were more cavities in the control group than in the others. We have hypothesized that children with renal transplant and those with chronic kidney disease are more likely to be closely followed up by physicians and dentists, which results in better health.

Our study has, however, some limitations. First, there is the fact that the research only evaluated the viral presence in saliva without quantifying it, so we could not distinguish between clinically relevant viral loads and very low viral concentrations or even latent virus DNA. Second, the nested PCR is very prone to cross-contamination. In order to reduce this risk, all samples were collected and manipulated according to strict criteria with the intention of avoiding contaminations. In addition, the samples were evaluated in triplicate in order to guarantee a greater trustworthiness of the data found. Finally, the size of our sample may have interfered with the results, but considering that the number of renal transplants in paediatric patients is very low, we can admit that the results found are important. Studies with other techniques, such as real-time PCR and involving viral quantification are important to reaffirm the results of this study.

Therefore, it can be concluded that the salivary shedding of HSV-1 and EBV in paediatric patients was more often found in renal transplant recipients than in renal failure and control children. Although our study design was not able to demonstrate causality, we could observe the presence of oral blisters in renal transplant recipients. In addition, transplanted recipients showed more oral manifestations than renal failure and control children. Taken together, these findings present a warning about the importance of following up these patients.

## Disclosure statement

The authors declare that they have no conflict of interest.

## ORCID

Rubens Caliento http://orcid.org/0000-0002-5152-124X
Dmitry José de Santana Sarmento http://orcid.org/0000-0001-7972-9141
Priscila Lie Tobouti http://orcid.org/0000-0003-1090-3900
Paulo Henrique Braz-Silva http://orcid.org/0000-0002-1842-9521
Marina Gallottini http://orcid.org/0000-0001-6071-5110

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