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Oropharyngeal candidiasis outcomes in renal transplant recipients receiving nystatin versus no antifungal prophylaxis

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Abstract

Objective: To compare the incidence of oropharyngeal candidiasis (OC), or thrush, in renal transplant recipients receiving nystatin versus no antifungal prophylaxis.

Methods: This was a single-center, retrospective, non-inferiority study of adult renal transplant recipients (RTRs) who received nystatin for 30 days for OC prophylaxis (nystatin group) or no antifungal prophylaxis therapy (No PPX group). The primary outcome was the incidence of OC within 3 months post-transplant. Secondary outcomes included time to OC occurrence and severity of OC. The pre-specified non-inferiority margin was 10%.

Results: The incidence of OC within 3 months post-transplant among 257 RTRs was 7.8% (10/128) in the No PPX group and 4.7% (6/129) RTRs in the nystatin group, a risk difference of 3.2% (95% CI, −2.7% to 9.1%, non-inferiority $P = .04$). The median time to OC was 7.5 days (IQR 6.3-34.3 days) in the nystatin group and 9.5 days (IQR 5.3-30.5 days) in the No PPX group ($P = .64$). Esophageal candidiasis was observed in 10% (1/10) of RTRs with OC in the No PPX group compared to 16.7% (1/6) RTRs in the nystatin group ($P = 1.00$). All RTRs with OC achieved symptom resolution with fluconazole and/or nystatin. Two patients in the No PPX group required readmission for decreased oral intake, and OC was diagnosed and treated during their hospital day.

Conclusions: In this retrospective study of adult RTRs, the absence of antifungal prophylaxis demonstrated non-inferiority to 30-day nystatin prophylaxis at reducing the incidence of OC within 3 months of transplant. OC prophylaxis may not be warranted after renal transplant.

KEYWORDS

antifungal prophylaxis, esophageal candidiasis, kidney transplant, nystatin, oropharyngeal candidiasis, renal transplant, thrush

1 | INTRODUCTION

Oropharyngeal candidiasis, or OC, is a fungal infection associated with immunosuppression among solid organ transplant recipients.[1-6] OC presents as soft yellowish-white plaques or diffuse erythematous patches on the oral mucosa, which can cause patients to experience a cottony feeling in the mouth, altered taste and sense of smell, odynophagia, and dysphagia.[4] OC development can predispose patients to more severe manifestations such as esophageal candidiasis and disseminated *Candida* infections.[7]

The incidence of OC among renal transplant recipients (RTRs) is variable. While early reports observed rates of up to 50% within 3 months post-transplant in RTRs not receiving prophylaxis, more recent studies reported rates below 10% in RTRs receiving modern immunosuppression.[1-3,5-8] This decline may be attributed to improved surgical techniques and immunosuppressive regimens which have reduced peri-transplant complications, need for broad-spectrum antibiotics, and length of hospital stays.[9] While OC rates are low in contemporary studies, there is limited evidence evaluating the risk of developing OC among RTRs in the absence of antifungal prophylaxis.

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend pharmacological prophylaxis against oral and esophageal *Candida* with clotrimazole lozenges, nystatin, or fluconazole for 1-3 months after renal transplant.[10] However, this recommendation is based on low-quality evidence, and these antifungal agents carry clinical challenges. As a class, azoles like fluconazole and clotrimazole inhibit CYP3A4 in the liver and gut, through which immunosuppressants like calcineurin inhibitors (CNI) are metabolized.[1,11,12] Azole initiation may lead to supratherapeutic CNI trough levels which increases the renal toxicity risk to the allograft, while the discontinuation of azoles could result in subtherapeutic levels and potentially cause allograft rejection.[1,11]

Unlike azoles, nystatin does not inhibit CYP3A4, and thus, is favorable from an interaction profile perspective. However, because of its unpalatable taste, complex administration (ie, swish and swallow), four times daily dosing, and the need to avoid eating and drinking after administration, patients have reported poor medication adherence to nystatin.[8] Several observational studies indicate that barriers to adherence and poorer quality of life are influenced by the complexity of drug regimens and increased dosing frequency of medications, ultimately emphasizing the urgency to simplify post-transplant medication regimens.[13-15]

One strategy of simplification was demonstrated by Guerra and colleagues, who questioned the need for prolonged antifungal prophylaxis. This group compared nystatin administered until time of discharge (average of 5.7 days of therapy) versus 30 days after transplant and observed no significant difference in the rates of OC (7.1% vs 0%, $P = .08$).[6] Although this study challenges commonly used strategies among RTRs that employ 1-3 months of antifungal prophylaxis, there is limited literature addressing the risk of developing OC in RTRs without pharmacologic prophylaxis in the modern era of immunosuppression and surgical advancements. Thus, our study investigated whether the omission of antifungal prophylaxis is associated with a clinically acceptable risk of OC development in RTRs. Our objective was to compare the incidence of OC in renal transplant recipients receiving nystatin versus no antifungal prophylaxis.

2 | METHODS

2.1 | Study design, population, and immunosuppression

This single-center, retrospective, non-inferiority study was approved by the institutional review board at the University of Michigan. Electronic medical records were screened to identify adult RTRs transplanted between February 1, 2018 and December 31, 2019 at the University of Michigan Transplant Center. Patients transplanted before the nystatin shortage in December 2018 were universally administered nystatin prophylaxis, and patients transplanted after February 14, 2019 universally received no OC prophylaxis. As a result, we were able to screen patients for study inclusion by transplant date. Thus, eligible patients were divided into the nystatin group (transplanted between February 1, 2018 and November 30, 2018) and the no prophylaxis (No PPX) group (February 14, 2019 to December 31, 2019). Across the two study periods, immunosuppression regimens were the same with the exception of a change in rabbit anti-thymocyte globulin (rATG) induction to living unrelated renal transplants (LURT). All LURT were administered rATG induction during the entire study period except from April 1, 2018 to March 31, 2019, during which the use of rATG was limited to high immunologic risk patients only because of a cost savings initiative.

Patients were excluded if they received systemic antifungal treatment for any indication other than OC, used an alternative antifungal agent for OC prophylaxis (eg, fluconazole), had less than 3 months of data after transplant because of death or lost to follow-up, had human immunodeficiency virus, received multi-organ transplants, or discharged on an immunosuppression other than tacrolimus, mycophenolate, and prednisone. Inpatient and outpatient electronic medical records were reviewed for patient baseline characteristics, which included demographics, comorbid conditions, tobacco and inhaled corticosteroid use, etiology for end-stage renal disease, and any documented history of OC. Transplant demographics included the surgery date, hospital admission and discharge dates, donor status, induction and maintenance immunosuppression therapy, and whether RTRs received nystatin or no antifungal prophylaxis therapy. Patients were asked to self-report adherence as part of their routine care. Notes from providers, nurses, social workers, and pharmacists were reviewed to determine if a patient reported any medication non-adherence or whether non-adherence was a concern as a result of memory or cognitive concerns, psychiatric conditions, uncontrolled diabetes, low health literacy, limited social support, vision or hearing impairment, or language barriers.

The primary outcome was oropharyngeal candidiasis within 3 months post-kidney transplant. The secondary outcomes were the time to OC occurrence (measured from the transplant date to the OC diagnosis date) and the severity of the OC, as measured by the presence of esophageal candidiasis and any readmission where treatment for OC was initiated or continued. The pharmacologic treatment for OC and patient response to the treatment were collected in RTRs with OC.

2.2 | OC prophylaxis and treatment

Prior to December 2018, nystatin 500 000-unit suspension four times daily for a total of 30 days was used per the institution protocol for OC prophylaxis in RTRs. Patients were instructed to orally swish nystatin for 15-30 seconds, swallow, and not to eat or drink for 15 minutes after taking nystatin. In response to a national shortage of nystatin starting December 3, 2018, the institution temporarily substituted fluconazole for antifungal prophylaxis therapy. Consequently, as a result of frequent supratherapeutic tacrolimus concentrations, the protocol was modified on February 14, 2019 to remove any antifungal agents for OC prophylaxis.

Diagnosis of OC was made if a provider documented plaque in the oral or esophageal mucosa on physical exam, clinically suspected OC based on signs and symptoms unexplained by other causes and prescribed antifungal treatment for OC with subsequent improvement. If there was appearance of esophageal candidiasis on esophagogastroduodenoscopy (EGD) exam and if symptoms improved on anti-fungal therapy, patients met criteria for clinical diagnosis of esophageal candidiasis. Selection of treatment agent was at the discretion of the provider.

2.3 | Statistical analysis

The study was designed to determine whether no antifungal prophylaxis would be non-inferior to nystatin prophylaxis. To satisfy the criterion for non-inferiority, the upper limit of a two-sided 95% confidence interval (CI) for the absolute difference between the two groups in the incidence of OC needed to be less than a predefined margin of 10%. The null hypothesis is that the risk difference is greater than or equal to 10%. A non-inferiority *P*-value of less than .05 will support the claim that the risk difference is less than 10%. A sample size of 118 patients in each group was needed to rule out an absolute increase of 10% in the incidence of OC at 3 months in the No PPX group with 90% power on the basis of a 3% incidence of OC at 3 months in the nystatin group. Baseline characteristics between the two groups were compared using chi-squared or Fisher's exact tests for categorical data. Student's *t* tests or Mann-Whitney *U* were used for continuous data. A *P*-value less than .05 was considered statistically significant. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS Version 26.0.; IBM Corp).

3 | RESULTS

Of 339 adult RTRs performed at the University of Michigan Transplant Center during the study period, a total of 257 RTRs were included in the analysis; 129 RTRs (50.2%) received nystatin prophylaxis; and 128 RTRs (49.8%) did not (Figure 1). Overall the two groups were well matched with regard to baseline characteristics (Table 1). Significantly more patients in the No PPX group received rATG induction compared to the nystatin group (72.7% vs 54.3%, $P = .003$),

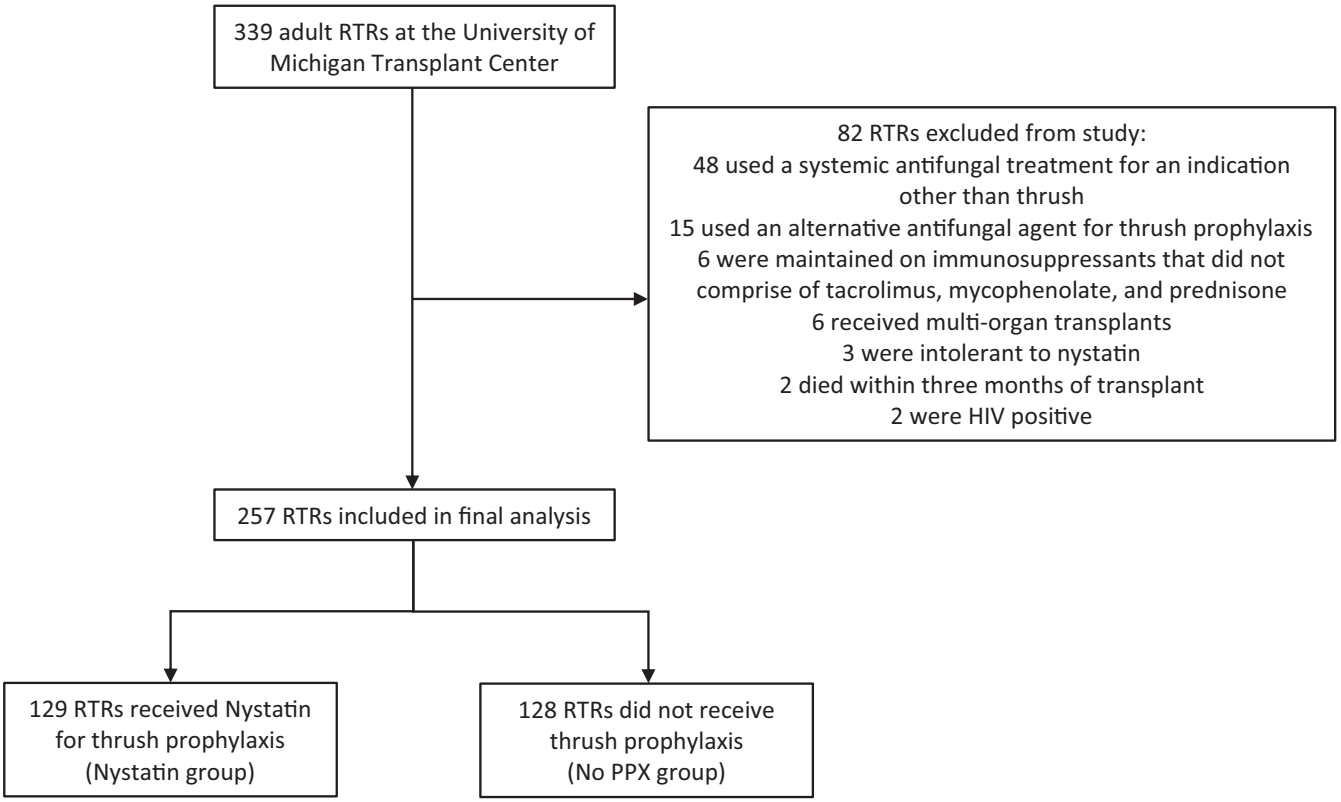

FIGURE 1 Flow chart outlining inclusion and exclusion criteria and different groups

TABLE 1 Baseline characteristics

	Nystatin (n = 129)	No PPX (n = 128)	*P*-value
Mean length of stay, days (SD)	4.4 (2.3)	4.5 (2.3)	.951
Mean age, years (SD)	52.1 (13.6)	53.5 (13.8)	.445
Male, n (%)	76 (58.9)	87 (68.0)	.155
Race, n (%)			
White	99 (76.7)	93 (72.7)	.650
Black	17 (13.2)	17 (13.3)	
Hispanic	8 (6.2)	11 (8.6)	
Asian	4 (3.1)	3 (2.3)	
Other	1 (0.8)	4 (3.1)	
Transplant etiology, n (%)			
Glomerulonephritis	11 (8.5)	8 (6.3)	.216
Diabetes	31 (24.0)	42 (32.8)	
Hypertension	11 (8.5)	20 (15.6)	
Polycystic kidney disease	16 (12.4)	14 (10.9)	
IgA-mediated nephritis	14 (10.9)	7 (5.5)	
Focal segmental glomerulosclerosis	5 (3.9)	5 (3.9)	
Other	41 (31.8)	32 (25)	
Mean peak Panel Reactive Antibodies, % (SD)			
Class I	13.0 (26.2)	8.6 (21.4)	.149
Class II	9.9 (23.6)	5.8 (18.5)	.125
Donor, n (%)			
Deceased	74 (57.4)	75 (58.6)	.982
Living, related	13 (10.1)	13 (10.2)	
Living, unrelated	42 (32.6)	40 (31.3)	
Dialysis prior to transplant, n (%)	99 (76.7)	90 (70.3)	.260
Median dialysis time, years (IQR)	2.8 (1.3-4.7)	3.0 (1.0-4.9)	.704
Induction, n (%)			
Antithymocyte globulin	70 (54.3)	93 (72.7)	.003
Basiliximab	2 (1.6)	0	
None	57 (44.2)	35 (27.3)	
History of candidiasis, n (%)	4 (3.1)	0	.122
Diabetes, n (%)	40 (31.0)	51 (39.8)	.153
Inhaled corticosteroid use, n (%)	4 (3.1)	5 (3.9)	1.00
Smoker, n (%)			
Current	5 (3.9)	3 (2.3)	.866
Former	48 (37.2)	49 (38.3)	
Never	76 (58.9)	76 (59.4)	
Rejection, n (%)	7 (5.4)	4 (3.1)	.540

Abbreviations: IQR, interquartile range; SD, standard deviation.

which reflects the change in the center practice during the study period. Known risk factors for OC,[2] including prevalence of diabetes mellitus (DM), inhaled corticosteroids (ICS) use, and smoking, were not significantly different between the two groups. No patients had documented candidiasis within 60 days prior to transplant.

Overall, 16 RTRs (6.2%) were clinically diagnosed with OC within 3 months post-transplant, with 10 in the No PPX group compared to 6 in the nystatin group (7.8% vs 4.7%, $P = .316$) (Table 2). The absolute difference in the incidence of OC was estimated to be 3.2% (95% CI, −2.7% to 9.1%, non-inferiority $P = .04$). The majority of OC cases (56.3%) were diagnosed within the first week after transplant. The median time to OC was not significantly different with 7.5 days (IQR 6.3-34.3 days) in the nystatin group and 9.5 days (IQR 5.3-30.5 days) in the No PPX group ($P = .64$).

TABLE 2 Primary and secondary outcomes

	Nystatin (n = 129)	No PPX (n = 128)	*P*-value
Thrush incidence, n (%)	6 (4.7)	10 (7.8)	.316
Median time to diagnosis, days (IQR)	7.5 (6.3-34.3)	9.5 (5.3-30.5)	.635
Esophageal candidiasis, n (%)	1 (16.7)	1 (10)	1.000
Readmission due to thrush, n (%)	1 (16.7)	2 (10)	1.000
Diabetes history, n (%)	40 (31)	51 (39.8)	.153
Thrush incidence, n (%)	2 (5)	7 (13.7)	.289

Abbreviation: IQR, interquartile range.

One patient in each group had EGD confirmed esophageal candidiasis: 10.0% in the No PPX group vs 16.7% in the nystatin group ($P = 1.00$). The patient in the No PPX group had invading fungal organisms found on biopsy. The patient in the nystatin group met diagnostic criteria for esophageal candidiasis based on EGD appearance and improvement after antifungal treatment, although biopsy and cytology results did not show evidence of fungal infection. Both patients were treated with fluconazole. Despite the two cases of esophageal candidiasis, no patients subsequently developed graft rejection or required a dose reduction in their immunosuppression medications. All patients with OC achieved symptom resolution with fluconazole (n = 10), nystatin (n = 3), or both (n = 3) treatments, and none died caused by OC or experienced rejection after treatment. Two patients in the No PPX group and one patient in the nystatin group required readmission because of the occurrence of OC.

A summary of the infected patients' characteristics is found on Table 3. None of the 16 patients who developed OC had a history of OC or smoking prior to transplant. Nine patients (56.3%) had DM and one patient (6.3%) used ICS before transplantation. Two OC cases were found among 40 diabetic patients in the nystatin group compared to seven among 51 diabetic patients in the No PPX group (5% vs 13.7%, respectively, $P = .289$). Of the RTRs with OC, 13 (81.3%) patients received induction therapy with rATG. Five patients (31.3%) were diagnosed during the index hospital stay with the longest duration of hospitalization being 14 days. For the three patients who were discharged more than 1 day after OC diagnosis, barriers to discharge included hiatal hernia, post-operative anemia requiring blood transfusion, prolonged QTc interval, or delayed graft function; OC was not the primary reason for prolonged length of stay in any of these patients. Only 19.7% of those infected had documented adherence concerns (20.0% in the No PPX group vs 16.7% in the nystatin group, $P = 1.00$). Among those who had medication adherence concerns, barriers documented in chart notes included stress, anxiety, depression, memory/cognitive problems, uncontrolled diabetes, and vision/hearing impairments.

4 | DISCUSSION

In this study, the absence of antifungal prophylaxis provided non-inferior 3-month OC outcomes compared to a 30-day nystatin regimen in renal transplant recipients. This finding was corroborated by an OC incidence in the No PPX group that was within 10% of the nystatin group and was observed despite significantly more patients in the No PPX receiving rATG ($P = .003$). Rates of OC at 3 months were low at 6.2% (16/257) in this cohort of RTRs maintained on a modern maintenance immunosuppression regimen of tacrolimus, mycophenolate, and prednisone. This is consistent with a similar single-center, retrospective study of adult RTRs, which found only 3 of 84 (3.6%) total OC cases in patients receiving nystatin for 30 days or only up until discharge.[6] Contrary to the 2009 KDIGO guidelines, this study found the risk of withdrawing antifungal prophylaxis in this patient population to be clinically acceptable.[10] It is important to note that KDIGO's recommendation for prophylaxis is based on studies from past decades, and thus this study complements the current body of literature surrounding the indication for OC prophylaxis in renal transplant patients on contemporary immunosuppression.[10]

A strength of this study is the design structured around the nystatin shortage, which allowed for a quasi-experimental design. Importantly, baseline characteristics between groups were similar, including usage of inhaled corticosteroids, history of diabetes, and history of candidiasis. Maintenance immunosuppression regimen was the same between groups. Notably, our institution temporarily stopped administering rATG induction to low immunologic risk LURT from April 1, 2018 to March 31, 2019, which resulted in 17 patients in the nystatin group to not receive rATG. In spite of this protocol change that drove more patients in the No PPX versus nystatin group to receive lymphocyte depleting induction, OC incidence was not significantly different between groups.

After solid organ transplant, patients are at greatest risk of developing OC within the first month, but OC can also present many months later.[16] In this study, the majority of affected patients developed OC within 1 month, with half the patients diagnosed within 1 week of transplant. The early onset of OC in some patients raises suspicion that OC was present prior to transplant, undiagnosed, and left untreated. While it is plausible that RTRs are likely colonized with oral *Candida*,[3,17] the prevalence of colonization in the RTRs of this study could not be confirmed as oral *Candida* cultures were not routinely obtained at time of transplant.

Established risk factors for OC include, but are not limited to, diabetes and smoking.[2] All patients who developed OC indicated having never smoked prior to transplant, and thus, this study cannot confirm smoking status as a risk factor. However, diabetes was a comorbid condition found in more than half (56.3%) of the RTRs who developed OC. One patient who was readmitted for OC was also found to have uncontrolled diabetes. Among patients who had a history of diabetes, there were a proportionately greater amount of OC cases in the No PPX group compared to the nystatin group, although the difference was not statistically significant ($P = .29$). Our study was not powered to evaluate the impact of withholding OC

TABLE 3 All thrush cases

Group	Age	Sex	LOS	Race	Cause	Donor	DM	ICS	Dialysis (y)	Induction
No PPX	57	F	4	H	PCKD	DDKT	Y	N	5.7	Y
No PPX	64	F	11	W	DM	DDKT	Y	N	2.1	Y
No PPX	59	M	5	B	DM	DDKT	Y	N	6	Y
No PPX	70	M	6	W	DM	LUKT	Y	N	0.83	Y
No PPX	64	F	6	W	Reflux nephropathy	DDKT	N	N	N/A	Y
No PPX	28	F	4	H	Lupus	LUKT	N	N	0.70	Y
No PPX	60	F	6	B	DM	DDKT	Y	N	6.67	Y
No PPX	35	M	7	H	DM	DDKT	Y	N	6.48	Y
No PPX	60	F	7	W	DM	DDKT	Y	N	4.52	Y
No PPX	64	M	4	W	Hepatorenal syndrome	DDKT	N	N	3.64	Y
Nystatin	55	M	4	W	Unknown	DDKT	N	N	2.42	N
Nystatin	70	F	14	W	Alport's syndrome	DDKT	N	Y	0.59	Y
Nystatin	34	F	8	W	Alport's syndrome	DDKT	N	N	N/A	Y
Nystatin	61	F	3	W	DM	DDKT	Y	N	6.05	N
Nystatin	58	F	7	W	Nephrotic syndrome	DDKT	Y	N	6.43	N
Nystatin	64	F	5	W	PCKD	DDKT	N	N	1.35	Y

Abbreviations: B, black; DDKT, deceased donor kidney transplant; DM, diabetes mellitus; F, female; H, hispanic; ICS, inhaled corticosteroid; LOS, length of stay; LUKT, living unrelated kidney transplant; M, male; N, no; N/A, not applicable; PCKD, polycystic kidney disease; rATG, rabbit anti-thymocyte globulin; TCMR, t-cell-mediated rejection; W, white; Y, yes.

prophylaxis in higher-risk sub-populations, and further investigation of prophylaxis strategies in patients actively smoking or with poor glycemic control may be warranted.

Esophageal candidiasis in renal transplant patients can sometimes be preceded by oral OC.[7] This study showed similar incidences of esophageal candidiasis in the No PPX group compared to the nystatin group (10% vs 16.7%, $P = 1.00$). Although there were two cases of esophageal candidiasis, graft rejection or dose reduction in immunosuppression medications was not observed. There was no observed association between OC and increased risk of subsequent rejection, and notably, all OC improved without needing to lower maintenance immunosuppression. Furthermore, all patients achieved symptom resolution with standard OC treatments and did not require a prolonged hospitalization because of OC. These findings suggest that the complications associated with OC may be acceptable without universal prophylaxis.

There are several limitations to this study. Given the retrospective, observational design of this single-center study, the attributable effect of nystatin cannot be fully determined. A larger randomized, controlled trial, where oral swabs are used to screen for candida colonization prior to transplant would be informative to determine the role of antifungal prophylaxis in colonized RTRs. Since our institution does not have a routine or formal screening process for OC in renal transplant recipients, some of the recorded cases relied on patients to self-report symptoms, which may have led to an underestimation of OC rates in both groups. The outcomes reflect RTRs who were managed by one immunosuppressive regimen strategy consisting of tacrolimus, mycophenolate, and prednisone. However, we expect that the difference in the incidence of OC among RTRs on a steroid-avoidance maintenance immunosuppressive regimen would be even smaller. The No PPX group was compared with only nystatin; therefore, no inference can be made for other antifungal prophylaxis agents. Meanwhile, all patients were followed for only 3 months post-transplant, yet studies indicate possible later development of OC.[16] Finally, this study did not formally evaluate adherence to medication regimens or measure quality of life.[3,9,16]

To our knowledge, this is the first adequately powered retrospective study to demonstrate non-inferiority of no antifungal prophylaxis compared to nystatin. The findings are similar to other studies that report low rates of OC and contribute to the body of evidence that challenges the absolute need for antifungal prophylaxis. Ultimately, this study has implications for renal transplant recipients that struggle with medication adherence and poorer quality of life owing to regimen complexity, inconvenient dosing frequency, polypharmacy, or the unpalatable taste of nystatin. Given the low incidence of OC, questionable benefit of antifungal prophylaxis, and continual efforts to simplify post-transplant medication regimens, we advocate that the

Rejection	Time since transplant (d)	Symptoms	Esophageal candidiasis	Treatment	Readmission	Adherence concerns
N	12	Epigastric pain	Y	Fluconazole	N	No
N	5	Dysphagia, odynophagia	N	Fluconazole	N	No
N	36	Odynophagia, heartburn	N	Fluconazole	Y, persistent	Yes
N	3	Dysphagia, odynophagia	N	Nystatin	N	No
N	14	Dry mouth; states feels like she has a film in her mouth; states brushes teeth several times throughout day	N	Fluconazole and nystatin	N, thrush x2	No
N	6	Odynophagia	N	Nystatin	N	No
N	7	Dysphagia, odynophagia, epigastric pain complicated by pancreatitis	N	Fluconazole and Nystatin	Y	No
N	4	Dysphagia, odynophagia, heartburn	N	Fluconazole	N	No
N	38	Dysphagia, odynophagia	N	Fluconazole and Nystatin	N	No
N	57	Not documented	N	Nystatin	N	No
N	43	Oral pain	N	Fluconazole	N	No
N	82	Dysphagia	N	Fluconazole	N, recurrent	No
N	8	Not documented	N	Fluconazole	N	No
TCMR, rATG	7	Dysphagia, severe esophagitis, and gastroparesis	N	Fluconazole	N, for rejection then thrush found	No
N	6	Dysphagia	Y	Fluconazole	Y	No
N	5	Presumed by MD, not documented	N	Fluconazole	N	No

elimination of OC prophylaxis after renal transplant is possibly clinically acceptable, although these results need to be confirmed by a randomized controlled clinical trial. In the absence of OC prophylaxis, we recommend educating patients to report any signs and symptoms of OC and visually examining the oral cavity at routine follow-up visits.

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CONFLICT OF INTEREST

No conflicts of interest to disclose.

AUTHORS CONTRIBUTIONS

TQK and LC: concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article. JMP: concept/design, data collection, data analysis/interpretation, critical revision of article. KAM: concept/design, data collection, critical revision of article. SMT and LJF: data collection, critical revision of article.

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