Seroprevalence of *Strongyloides stercoralis* and Evaluation of Universal Screening in Kidney Transplant Candidates: A Single-Center Experience in Houston (2012–2017)

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Background. Disseminated strongyloidiasis in solid organ transplant recipients is a rare but devastating infection. In our center, we implemented a universal screening of all candidates for kidney transplantation. We assessed the seroprevalence and utility of universal screening for strongyloidiasis in our center.

Methods. Patients were identified from our transplant referral list (from July 2012 to June 2017). Demographics, pretransplant laboratory, and serological screenings were retrospectively collected. For *Strongyloides*-seropositive (SSp) patients, data on travel history, symptoms, treatment, and stool ova and parasite examinations were extracted. Logistic regression and multiple imputation for missing data were performed.

Results. A total of 1689 patients underwent serological screening, of whom 168 (9.9%) were SSp. Univariate analysis revealed that SSp patients had higher rates of eosinophilia, diabetes mellitus, latent tuberculosis and were likely to be either Hispanic or Asian (*P* < .05). In multivariate analysis, eosinophilia (*P* = .01), diabetes mellitus (*P* = .02), and Asian race (*P* = .03) were associated with being SSp, but 45 (27%) of the SSp patients did not have any of these 3 factors, and 18 SSp patients (11%) had no epidemiological risk factors. All patients received ivermectin, and none developed disseminated strongyloidiasis. Of patients who underwent serological screening on multiple occasions, 6.8% seroconverted while waiting for kidney transplantation.

Conclusions. We found a high rate of *Strongyloides* seropositivity among our kidney transplantation candidates. No epidemiological risk factors effectively predicted SSp status in our population, and universal screening identified a large number of patients without such factors. Serial screening should be considered when a long wait time is expected before transplantation.

Key words: kidney transplant candidate; pretransplant screening; strongyloidiasis.

Strongyloides stercoralis is an intestinal parasite with an estimated 30–100 million infected individuals worldwide, mainly in the tropical, subtropical, and warm temperate regions [1]. In the United States, the prevalence is reported to be <6%, mostly in the southeastern United States and higher among immigrants, yet data in Texas are scarce [1, 2]. The filariform larvae of *S. stercoralis* infect humans by penetrating exposed skin through contaminated soil or through ingestion and are then transported to the lungs through the bloodstream [1–4]. Once fully developed inside the host, they cause a chronic gastrointestinal (GI) infection that persists for several decades with few or no symptoms

[3, 5]. In the immunocompromised population, such as solid organ transplant recipients, chronic strongyloidiasis may cause hyperinfection or disseminated diseases, with a high mortality rate, ranging from 50% to 89% [3, 6, 7].

Factors associated with *Strongyloides* infection include alcoholism, steroid use, and human T-cell leukemia virus infection [8–10]. In addition, disseminated infections or hyperinfections have been reported among patients with human immunodeficiency virus [11]. Although the primary cause of disease and death in solid organ transplant recipients is thought to be a reactivation and autoinfection from chronic or latent infection, there are documented reports of donor-derived infections [14, 15].

Solid organ transplant societies currently recommend targeted screening based on patients' epidemiological risks [16–18]. However, the definition of "endemic region" for strongyloidiasis in the guidelines is unclear. Certain parts of the Appalachian and southeastern United States are considered endemic areas [4, 19]. In Memorial Hermann Hospital renal transplant center in Houston, Texas, after a case of disseminated strongyloidiasis, we instituted a universal (nontargeted) screening for chronic *S. stercoralis* infection using an enzyme-linked immunosorbent

assay (ELISA) for *Strongyloides* antibody, because data regarding the endemicity of *Strongyloides* in our area are scarce and targeted screening may be difficult owing to the blurring between rural and urban populations. The aim of this study was to describe the seroprevalence of *S. stercoralis* among potential kidney transplant recipients and to evaluate the utility of *Strongyloides* universal screening in our center in Houston.

MATERIALS AND METHODS

After receiving approval from the institutional review board at the University of Texas Health Science Center at Houston, we obtained patient identification numbers from our kidney transplant referral database for the period of July 2012 to June 2017. All patients referred to our transplant center for renal transplant were screened for *S. stercoralis* infection using commercial ELISA tests. One of 2 ELISA kits was used for screening, depending on the study period: the Bordier-ELISA kit (Bordier Affinity Products) (sensitivity, 83%–89%; specificity, 97%–98%) or the Microwell ELISA kit (SciMedix or New Life Diagnostics) (referred to as IVD-ELISA in published studies [20, 21]; sensitivity, 89%–91%; specificity, 97%–99%), which detect antibodies against *Strongyloides ratti* antigens and *S. stercoralis* larval (L3) antigens, respectively. The blood samples were obtained in our transplant center.

We retrospectively reviewed patients' demographics, including ethnicity/race, country of origin, transplant type, pretransplantation screening tests for infectious diseases (cytomegalovirus immunoglobulin G, human immunodeficiency virus, syphilis, tuberculosis screening with interferon γ release assay [either QuantiFERON-TB Gold In-Tube or T-SPOT.TB test], and Epstein-Barr virus immunoglobulin G), and the presence of eosinophilia (>0.5 K/mL). For patients with who were seropositive, the presence of GI symptoms, travel history, and treatment type were collected from the medical records. Some patients underwent multiple screenings for *Strongyloides*. In those with positive serological results, we collected data from the time of the positive result, and in those with only negative results, we collected data from the time of the first negative result. However, those multiple serological results were used to identify patients who seroconverted. Furthermore, patients were grouped into *Strongyloides*-seropositive (SSp) and *Strongyloides*-seronegative (SSn) groups.

Descriptive statistics were used to summarize demographic data and clinical characteristics. Continuous variables are presented as mean or median with range, and categorical data as frequency and percentage. Wilcoxon rank-sum tests and χ^2 or Fisher exact tests were used to compare continuous and categorical variables, respectively. Variables showing a difference in the univariate analysis with a *P* value <.05 were included in the logistic regression model. All tests were 2 sided with a significance level of .05. Bootstrapping was performed to estimate the

internal validity of the regression model. Because a significant proportion of SSn patients had missing data for their county of origin, multiple imputation was used to obtain 5 imputed data sets for the supplementary analysis. The imputation model included age, ethnicity/race, diabetes mellitus (DM), eosinophilia, and latent tuberculosis. Data analysis was performed using IBM SPSS Statistics for Windows software, version 24 (IBM)

RESULTS

Our center received 2474 referrals for kidney transplantation during the period of July 2012 to June 2017; 1689 (68%) of the patients underwent pretransplantation screening, with 270 patients receiving kidney transplants during the studied period. Since the implementation of the screening and preemptive treatment with ivermectin, we have not encountered any disseminated or hyperinfection strongyloidiasis in our kidney transplant recipients.

Table 1 shows patients' baseline characteristics, country of origin, comorbid conditions, and pretransplantation serological results. A total of 1689 patients underwent pretransplantation *S. stercoralis* screening, with 617 (36.5%) having multiple *Strongyloides* serological tests performed during the study period. A total of 168 screened patients (9.9%) were SSp; 40 of the 168 underwent kidney transplantation. There was no statistically significant difference between the SSp and SSn groups regarding their median age (52 years) or sex distribution (61% male). Hispanic and Asian patients were more likely to be SSp (*P* = .04), but there was no significant difference in country of origin between the 2 groups. SSp patients were more likely than SSn patients to have DM (108 [64%] vs 828 [54%], respectively; *P* = .01) or eosinophilia (33 [20%] vs 192 [13%]; *P* = .02) and more likely to have a positive results of tuberculosis screening with interferon γ release assay (21 [13%] vs 107 [8%]; *P* = .01).

Data on country of origin were available in 1075 patients (63.6%). The majority of patients were from the United States (84 [58%] SSp and 571 [61%] SSn patients), with 49 [34%] SSp and 263 (28%) SSn patients from Mexico, Central or South America, or the Caribbean, and 11 (8%) and 58 (6%), respectively, from Asia. Only 9% of SSp patients had GI symptoms (Table 2).

Multivariate logistic regression analysis (Table 3) shows that eosinophilia (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.1–2.7; *P* = .01), DM (1.5; 1.1–2.1; *P* = .02), and Asian race (2.7; 1.1–6.4; *P* = .03) were associated with being SSp. However, 45 SSp patients (27%) did not have any of these 3 factors. Eighteen SSp patients (11%) did not have any epidemiological risk factors used in a targeted screening, such as history of residence in or travel to the known endemic countries. Separate logistic regression analysis was conducted after multiple imputation for missing data, showing results similar to the original analysis

Table 1. Baseline Characteristics, Country of Origin, Comorbid Conditions, and Pretransplantation Serological Results in 1689 Solid Organ Transplant Candidates Undergoing Screening for *Strongyloides*

Characteristic	Patients, No./Total (%)[a]		*P* Value
	SSp (n = 168)	SSn (n = 1521)	
Male sex	102/168 (61)	936/1521 (61)	.84
Age, median (IQR), y	52 (41–60)	52 (45–60)	.21
Ethnicity/race			
Hispanic	56/168 (33)	426/1521 (28)	.04[b]
Non-Hispanic white	26/168 (16)	309/1521 (20)	
African American	45/168 (27)	500/1521 (33)	
Asian	9/168 (5)	40/1521 (3)	
Other	32/168 (19)	246/1521 (16)	
Country/region of origin[c]			
United States	84/145 (58)	571/935 (61)	.12
Mexico, Central/South America, or the Caribbean	49/145 (34)	263/935 (28)	
Asia	11/145 (8)	58/935 (6)	
Other	1/145 (1)	38/935 (4)	
Comorbid condition			
Cirrhosis	4/168 (2)	43/1521 (3)	.73
Diabetes mellitus	108/168 (64)	828/1521 (54)	.01[b]
Hypertension	153/168 (91)	1323/1521 (87)	.13
HIV infection	4/168 (2)	37/1521 (2)	.96
Type of transplantation[d]			
Kidney	166/168 (99)	1463/1521 (96.2)	.36
Kidney and pancreas	2/168 (1)	47/1521 (3)	
Pancreas	0	1/1521 (0.1)	
Other[e]	0	10/1521 (0.7)	
Positive pretransplantation serological results			
Syphilis screening	9/168 (6)	88/1521 (6)	.9
Latent tuberculosis screening[f]	21/161 (13)	107/1432 (8)	.01[b]
CMV IgG	142/168 (85)	1198/1521 (79)	.08
EBV IgG	162/163 (99)	1484/1511 (98)	.40
Hepatitis C screening	13/168 (8)	98/1521 (6)	.46
Eosinophilia	33/168 (20)	192/1521 (13)	.02[b]

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IQR, interquartile range; SSn, *Strongyloides*-seronegative; SSp, *Strongyloides* seropositive.

[a]Data represent no./total (%) of patients unless otherwise specified; denominators (totals) vary according to availability of data.

[b]Significant at *P* < .05.

[c]Data were missing for a significant number of patients in the SSn group, because their country of origin was not routinely documented.

[d]The type of transplantation for which patients were referred.

[e]The "Other" category includes combined transplants (eg, liver and kidney).

[f]Patients with indeterminate results were excluded from analysis.

(Supplementary Table 1). Only 1 of the 42 patients (2%) who underwent stool ova and parasite tests had a positive stool result for *S. stercoralis* larvae.

All SSp patients were treated before undergoing transplantation. The treatment regimen was available in 92 of the 168 patients (55%), who took 200 µg/kg of ivermectin orally in 2 separate doses; 67 of 92 (72%) took daily doses over 2 consecutive days, and 14 (15%) received 2 doses 1 week apart.

Pretransplantation serological screenings are annually repeated in our center. Of 617 patients who underwent multiple *S. stercoralis* serological tests, 42 (6.8%) seroconverted. Table 4 shows the characteristics of patients who seroconverted from seronegative to seropositive over the observed period. The majority of seroconverted patients were born in the United States (58%), with 3 of them having no history of travel outside the United States.

DISCUSSION

To our knowledge, this is the largest study that has evaluated the seropositivity and universal (nontargeted) screening for chronic *S. stercoralis* infection among patients referred for a kidney transplant in the United States. We found that 9.9% of the screened kidney transplant candidates in the Houston area were seropositive for *S. stercoralis* infection. In addition, our data suggest that targeted screening for strongyloidiasis may fail to identify a significant proportion of SSp patients in

Table 2. Travel History, Gastrointestinal Symptoms, and Treatment History in 168 *Strongyloides* Seropositive Patients

Characteristics	SSp Patients, No. (%)
Travel history	
None	20/79 (25)
Mexico, Central America, or the Caribbean	47/79 (60)
Asia	10/79 (13)
Other	2/79 (3)
Gastrointestinal symptoms	14/153 (9)
Abdominal pain	2/153 (1)
Nausea	1/153 (1)
Diarrhea	10/153 (7)
Other	1/153 (1)
Ivermectin treatment regimen[b]	
Once daily for 2 d	67/92 (72)
Once weekly for 2 doses	14/92 (15)
Other regimen	6/92 (7)

Abbreviation: SSp, *Strongyloides*-seropositive.

[a]Data represent no./total (%) of patients; denominators (totals) vary according to availability of data.

[b]All were treated with ivermectin, of whom 92 patients had documented treatment regimens.

Table 4. Characteristics of Patients Who Seroconverted After Initially Negative *Strongyloides* Serological Results

Characteristics	Patients Who Serocoverted to SSp, No. (%)[a] (n = 42)
Male sex	25/42 (59)
Age, median (IQR), y	52 (44–58)
Ethnicity/race	
Hispanic	14/42 (33)
Non-Hispanic white	5/42 (12)
African American	16/42 (38)
Asian	2/42 (5)
Other	5/42 (12)
Country/region of origin	
United States	19/33 (58)
Mexico, Central/South America, or the Caribbean	11/33 (33)
Asia	2/33 (6)
Other	1/33 (3)
Travel history	
None	3/16 (19)
Mexico/Central America	11/16 (69)
Other	2/16 (12)

Abbreviations: IQR, interquartile range; SSp, SSp, *Strongyloides* seropositive.

[a]Data represent no./total (%) of patients unless otherwise specified; denominators (totals) vary according to availability of data.

our pretransplant population because many of these patients had none of the epidemiological risk factors used in targeted screening.

S. stercoralis transmission from a donor has been reported in solid organ transplant recipients. Hamilton et al [22] reported 2 cases involving kidney transplants in which the donor, who was born in the Dominican Republic, had received steroid therapy before procurement of the organs. There are other published cases reporting donor-derived strongyloidiasis in recipients of intestinal and liver transplantation involving donors coming from endemic areas (Honduras and Ecuador) [14, 23].

A study by the New York Organ Donor Network of targeted screening in donors with previous residential histories in the endemic area, from 2010 to 2013, found that only 10 of 233 consented potential donor (4.3%) were positive at ELISA for *S. stercoralis* antibody against crude antigen [15]. Because 6

Table 3. Baseline Factors Associated With Seropositivity for *Strongyloides* at Logistic Regression Analysis[a]

Characteristic	OR (95% CI)	P Value
Ethnicity/race		
Hispanic	1.4 (.86–2.4)	.16
Non-Hispanic white	Reference	…
African American	1.1 (.7–1.9)	.7
Asian	2.7 (1.1–6.4)	.03[b]
Others	1.5 (1.1–2.7)	.1
Diabetes mellitus	1.5 (1.1–2.1)	.02[b]
Eosinophilia	1.7 (1.1–2.7)	.01[b]
Positive at latent tuberculosis screening	1.6 (.9–2.7)	.06

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Validated by bootstrap analysis.

[b]Significant at *P* < .05.

of 7 reported donors were born in Latin America, the authors concluded that targeted donor screening can avert donor-derived transmission [15]. However, our data elucidated the difficulty of targeted screening in our population, because a high proportion (22%) of SSp patients were born in the United States and denied any travel histories. Furthermore, 18 SSp patients (11%) and 3 of 16 (19%) who seroconverted (from negative to positive) during the study period did not have any epidemiological risk factors, which indicates that indigenous cases may exist in our area, as shown in a prior report from rural Kentucky's Appalachian regions, with a prevalence of 1.9% [2].

One of the challenges in chronic strongyloidiasis is the diagnostic methods. Because the microscopical stool examination method has a low yield, serological tests are generally recommended for the screening before the transplantation [17]. However, the sensitivities and specificities vary among different *Strongyloides* serological tests, and there is concern about possible false-positivity. During our study period, we used 2 kinds of ELISA kits (Bordier-ELISA and Microwell ELISA). The use of *S. ratti* larval antigens may have a slightly lower sensitivity because of incomplete cross-reactivity of both *Strongyloides* species. The tests are less specific in the presence of other helminthic infections; however, the ova and parasite examinations did not detect other parasitic infections in our cohort. To improve specificity, different diagnostic platforms as well as new antigens, such as recombinant antigen derived from *S. stercoralis*, have been studied. Among patients with culture- or smear-proven *Strongyloides* infection, a previous study

indicated that new methods improve specificity but may decrease sensitivity (NIE luciferase immunoprecipitation system assay; sensitivity, 85%; specificity, 100%), and these might not be the best screening methods [20]. In addition, none of the new tests are currently available commercially for use in the United States.

We identified several variables and risk factors associated with increased risk of *S. stercoralis* infection. Analysis of available data concerning country of origin, ethnicity/race, and travel history showed a significant increase in the risk of *S. stercoralis* infection in the Asian population with an OR of 2.7; six of the Asian SSp patients with a documented travel history reported travel outside the United States.

Overall, unlike in previous reports of increased risk of *S. stercoralis* infection in the immigrant population [1, 8], we did not find a difference between SSp and SSn groups with regard to country of origin. This could be owing to missing data in 41% of SSn and 14% of SSp patients. To support our findings, we conducted logistic regression after supplementing missing data with multiple imputation, and this analysis revealed similar results compared with the original analysis. Unfortunately, most of the SSn patients lacked documentation of travel history, which was not routinely documented in the transplant candidates, precluding statistical analysis of this aspect.

We also investigated the relationship between DM and strongyloidiasis because previous reports have suggested contradictory associations. Data from diabetic patients residing in a *Strongyloides*-endemic region indicated an increased risk of infection in these patients (OR, 3.9; 95% CI, 1.6–15.9; $P < .05$) [12]. In contrast, another study of the aboriginal population in Australia found that DM as a factor was inversely associated with *Strongyloides* infection (adjusted OR, 0.39; 95% CI, .23–.67; $P = .001$) [13]. In our studied population, we found a significantly increased risk of strongyloidiasis in diabetic patients (OR, 1.5; 95% CI, 1.1–2.1; $P = .01$).

Eosinophilia was an independent factor associated with strongyloidiasis, as expected, in the multivariate analysis, with an increased OR (1.7; 95% CI, 1.1–2.7; $P = .01$) and with a prevalence of 20% among SSp patients. Therefore, about 80% of SSp patients did not exhibit eosinophilia at the time of screening. Prior studies have reported a prevalence of eosinophilia ranging from 20% to 80% in patients with strongyloidiasis [24, 25]. We hypothesize that several factors could have affected our results, such as the variability in the timings when eosinophil counts were measured, the burden of disease, or differences between acute and chronic strongyloidiasis cases.

Strongyloidiasis can present with diarrhea, abdominal pain, and skin manifestations, but it is often asymptomatic, especially in chronic infections [3]. However, because data shedding light on the frequency of GI symptoms are lacking, we investigated the frequency of such symptoms in the SSp group at the time of screening, and we found that only 9% of our SSp patients reported GI symptoms, mostly chronic or recurrent diarrhea (7%). Therefore, although GI symptoms should be considered when testing for *S. stercoralis*, the majority of patients were not symptomatic.

Among the patients who had 3 consecutive ova and parasite stool tests, only 1 patient (2%), born in Vietnam, had a positive result. Although not all SSp patients underwent ova and parasite stool examination, our data reflected a low yield of this test in our studied population. The low sensitivity of this conventional method has prompted some investigators to use other techniques (agar plate culture, Baermann technique) reported to be more sensitive, but such methods take a long time to obtain results and require trained personnel [3, 26]. Promising new diagnostic tests such as polymerase chain reaction could provide a rapid and reliable result in the future, with reported sensitivity ranging from 56% to 72% [27–29]. Such tests are not yet approved or commercially available for diagnostic use.

All of the patients received ivermectin for strongyloidiasis treatment, which is the most effective available therapy for this condition [30, 31]. There is no specific recommendation regarding how to monitor therapeutic response. Some studies suggest seroconversion (positive to negative) 6–12 months after therapy [32, 33]. However, we did not investigate this aspect in our study because its clinical significance is unknown. The optimal therapeutic regimen for *Strongyloides* in pretransplantation prophylaxis is undetermined. The guidance for a living-kidney transplant donor recommends 200 µg/kg doses either on 2 consecutive days or 2 weeks apart [18]. However, another guideline recommends a regimen that is 2 weeks apart, considering the theoretical advantage in the "autoinfective cycle" of *Strongyloides* [34]. Both regimens seemed to work effectively in multiple previous studies, and no direct comparison between regimens was made in those studies [31]. A 2018 study described the poor efficacy of ivermectin therapy against *Strongyloides,* reporting persistent *Strongyloides* positivity after treatment [35], but these results were questioned owing to a small sample size and significantly high rates of treatment failure [36].

A significant number of our patients (6.8%) had seroconversion (negative to positive) during the study period, which suggests that serial serological screening may be required if the patients stay on the transplant waiting list for prolonged periods. This also raises the question of the optimal frequency of screening and the potential for new exposures before or after transplantation. Furthermore, most of those patients had a notable travel history to endemic regions. However, 3 of 16 patients were born in the United States and had denied any travel history, suggesting indigenous acquisition of *S. stercoralis* infection. Further studies are warranted to address those issues.

Finally, we screened our living donors for strongyloidiasis, but we did not implement this screening among deceased donors. However, a recent study from Miami, Florida, showed a prevalence of 3.9% of strongyloidiasis in the deceased donor

population [37]. The implementation of deceased donor screening should be carefully considered in our area based on endemicity and potential impact on the screening process [19]. As of now, we have not encountered any disseminated or hyperinfection cases in our transplant center since implementing pretransplantation universal screening and ivermectin therapy.

Out study has limitations. First, it had a retrospective design, which could lead to selection bias, and we also encountered missing data; however, we evaluated the latter with statistical analysis using multiple imputation, which did not show any difference from previously concluded results. Second, as discussed above, the currently available tests have some limitation in their sensitivity and specificity for the diagnosis of strongyloidiasis. Finally, our study cannot conclude the superiority of universal serological screening over targeted screening, because it was a noncomparative study. Ideally, a comparative study should be conducted to demonstrate that universal screening decreases the incidence of disseminated infection. However, it would be difficult to conduct owing to the low incidence of disseminated infection. We also lack comprehensive data regarding the general prevalence of *Strongyloides* in the southern states of the United States, to exclude the possibility of endemicity.

To conclude, we found that 9.9% of screened candidates for kidney transplantation in Houston, Texas, were SSp. No factors effectively predicted this result in our population. The universal screening identified a significant number of SSp patients without epidemiological risk factors, which suggests possible local acquisition of the infection. Serial screening should be considered when patients are expected to have a long wait before transplantation in populations similar to ours.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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