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The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

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Abstract

Background: Invasive candidiasis (IC) is a common cause of mortality in solid organ transplant recipients (OTRs), but knowledge of epidemiology in this population is limited.

Method: The present analysis describes data from 15 US centers that prospectively identified IC from nearly 17 000 OTRs. Analyses were undertaken to determine predictors of infection and mortality.

Results: A total of 639 cases of IC were identified. The most common species was *Candida albicans* (46.3%), followed by *Candida glabrata* (24.4%) and *Candida parapsilosis* (8.1%). In 68 cases >1 species was identified. The most common infection site was bloodstream (44%), followed by intra-abdominal (14%). The most frequently affected allograft groups were liver (41.1%) and kidney (35.3%). All-cause mortality at 90 days was 26.5% for all species and was highest for *Candida tropicalis* (44%) and *C. parapsilosis* (35.2%). Non-white race and female gender were more commonly associated with non-*albicans* species. A high rate of breakthrough IC was seen in patients receiving antifungal prophylaxis (39%). Factors associated with mortality include organ dysfunction, lung transplant, and treatment with a polyene antifungal. The only modifiable factor identified was choice of antifungal drug class based upon infecting *Candida* species.

Conclusion: These data highlight the common and distinct features of IC in OTRs.

KEYWORDS

Candida, solid organ transplant

1 | INTRODUCTION

Advances in transplantation biology, organ procurement, surgical techniques, and immunosuppressive therapy have made organ transplantation an effective option for the management of organ failure, with a 1-year survival >60%-80%. However, infection remains one of the most challenging complications of solid organ transplantation.[1–5] The most prevalent mycosis is invasive candidiasis (IC) and is associated with considerable mortality.[6–13] An understanding of the epidemiology and organ transplant type-specific risk factors and outcomes may identify effective prevention and treatment strategies.

The Transplant-Associated Infection Surveillance Network (TRANSNET) was established in 2001 as a prospective surveillance group for the purpose of understanding the burden of invasive fungal infections, and to better define patients at risk and outcome of these infections.[14,15] The group included 15 geographically diverse transplant centers in the United States that provided infection surveillance data for invasive fungal infections in solid organ transplant recipients (OTRs). The emphasis of this report is to examine the epidemiology and outcomes of IC.

2 | METHODS

2.1 | Study population

Fifteen TRANSNET sites performed transplantation and provided prospective surveillance on these patients. The period of IC infection surveillance was 2001 through 2006, and included all OTRs who developed an IC infection during this period. Information collected on patients included demographics (age, gender, race/ethnicity) and type of transplant. Follow-up information for the cohort was gathered to obtain date of last follow-up and patient status (alive or dead).

2.2 | Definitions and case identification

Only proven and probable IC infections as defined by the EORTC/MSG criteria[16,17] were included (see definitions in supplemental Data S1). Lower urinary tract infection and mucosal infections were excluded. Cases were reviewed to determine individual case validity by a Data Review Committee. IC was identified prospectively among this population by establishing monthly patient logs of transplant recipients, reviewing pertinent culture data and histopathology, as well as through the routine contact with transplant physicians and coordinators. Case information included infection site, culture data, method of diagnosis, date and type of transplant, history of rejection, comorbid conditions, cytomegalovirus infection (based on tissue histopathology or viremia), recent immunosuppressive and antifungal treatment data, and patient status at least 3 months after initial diagnosis of IC infection.

2.3 | Microbiologic methods

Available cultures and histopathological specimens were processed at the participating hospitals. Species identification was performed using routine methods at the participants' affiliated laboratories. Available fungal isolates were forwarded to the Centers for Disease Control Mycotic Diseases Branch for confirmation of identification.

2.4 | Data analysis

Univariate analyses to assess the relationship between variables and survival were performed by tabulating these measures in the survivor and non-survivor cohorts. The χ^2 test or the Fisher exact test was used to assess statistical significance for categorical variables and the Wilcoxon rank-sum test was used for continuous variables. Multivariable analyses of factors associated with mortality were performed using stepwise multiple logistic regression via generalized estimating equations. We chose to model the correlation of the repeated measures on some of the individuals with a compound symmetry covariance structure. The criterion for entry into the model was significant at α=.20, whereas the criterion for remaining in the model was significant at α=.05. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. A multiple logistic regression model containing the best predictor variables obtained from the stepwise analysis was then run using all available data in order to obtain more robust estimates of the ORs, 95% CIs, and *P*-values. Once final models were achieved through the stepwise process, a potential interaction between prednisone use and rejection was evaluated by incorporating an interaction term into the final model.

A time-to-death analysis was also performed. First, a univariate analysis comparing transplant type, and another comparing *Candida* species were conducted via Kaplan–Meier estimation and the log-rank test. To validate the above logistic regression results, multivariate analyses were run using Cox regression incorporating the final model terms found in logistic models. All statistical tests were 2-tailed and were performed using a 5% significance level (α=.05). Statistical analyses were performed using the R statistical computing environment, version 2.11.

3 | RESULTS

3.1 | Epidemiology of IC among OTRs

A total of 639 cases of IC (533 proven and 106 probable) occurred in 594 OTRs from among nearly 17 000 patients under surveillance in the study period. The demographic characteristics, transplantation type, and survival in OTRs with IC overall, by transplant type, and *Candida* species, are presented in Table 1. The rank order of most frequently encountered species was *Candida albicans* (46.3%), followed by *Candida glabrata* (24.4%), and *Candida parapsilosis* (8.1%). In 68 cases >1 *Candida* species was involved in IC. The most common site of IC was bloodstream in 44% of cases, followed by intra-abdominal infection (14%). Among the 635 OTRs with IC, infection was observed most commonly in liver (261, 41.1%), followed by kidney (224, 35.3%), kidney-pancreas (58, 9.1%), and lung (55, 8.7%) (4 cases were missing organ type classification). The median time to onset for IC was 80 days post transplantation (interquartile range [IQR] 14-545 days). In total, 205 infections were diagnosed early post transplant (within

TABLE 1 Characteristics of OTRs with invasive candidiasis infections: univariate analysis based upon *Candida* species

Variable	All species N (%)	*C. albicans* 296 (46.3)	*C. glabrata* 156 (24.4)	*C. krusei* 20 (3.1)	*C. parapsilosis* 52 (8.1)	*C. tropicalis* 25 (3.9)	Other	Multiple 68 (10.6)	Non-*albicans*	*P*-value[1]
Demographics										
Age, mean±SD	47.4±15.7	47.3±15	49.6±13.1	41.5±20.9	40.3±22	50.6±16.7	44.4±18.6	49.9±14.1	46.8±16.9	.17
Male	361 (57.0)	185 (62.7)	72 (46.5)	1019 (52.6)	33/50 (66.0)	12/24 (50.0)	13/22 (59.1)	36/68 (52.9)	134/261 (51.3)	.03
Female	272 (43.0)	110 (37.3)	83 (53.5)	9/19 (47.4)	17/50 (34.0)	12/24 (50.0)	9/22 (40.9)	32/68 (47.1)	110/295 (37.3)	
Race										
Caucasian	502/611 (82.2)	242/282 (85.8)	121/150 (80.7)	15/20 (75.0)	34/47 (72.3)	15/24 (62.5)	15/21 (71.4)	60/67 (89.6)	194/254 (76.4)	.01
Black	79 (12.4)	26 (8.8)	24 (15.4)	3 (15.0)	9 (17.3)	8 (32.0)	4 (18.2)	5 (7.4)	26 (8.8)	
Other	58 (9.1)	28 (9.5)	11 (7.1)	2 (10.0)	9 (17.3)	2 (8.0)	3 (13.6)	3 (4.4)	28 (9.5)	
Organ										
Heart	48/635 (7.6)	25/294 (8.5)	9/155 (5.8)	2/20 (10.0)	5/52 (9.6)	1/25 (4.0)	3/21 (14.3)	3/68 (4.4)	19/265 (7.2)	.63
Lung	55/635 (8.7)	30/294 (10.2)	9/155 (5.8)	0/20 (0.0)	6/52 (11.5)	6/25 (24.0)	1/21 (4.8)	3/68 (4.4)	21/265 (7.9)	.03
Pancreas	38/635 (6.0)	18/294 (6.1)	13/155 (8.4)	1/20 (5.0)	3/52 (5.8)	0/25 (0.0)	0/21 (0.0)	3/68 (4.4)	17/265 (6.4)	.56
Small bowel	9/635 (1.4)	2/294 (0.7)	4/155 (2.6)	1/20 (5.0)	1/52 (1.9)	1/25 (4.0)	0/21 (0.0)	0/68 (0.0)	7/265 (2.6)	.32
Kidney	224/635 (35.3)	95/294 (32.3)	62/155 (40.0)	6/20 (30.0)	22/52 (42.3)	7/25 (28.0)	11/21 (52.4)	21/68 (30.9)	103/265 (38.9)	.25
Liver	261/635 (41.1)	124/294 (42.2)	58/155 (37.4)	10/20 (50.0)	15/52 (28.8)	10/25 (40.0)	6/21 (28.6)	38/68 (55.9)	98/265 (37.0)	.05
Kidney-pancreas	58/635 (9.1)	27/294 (9.2)	18/155 (11.6)	1/20 (5.0)	3/52 (5.8)	1/25 (4.0)	2/21 (9.5)	6/68 (8.8)	24/265 (9.1)	.8
Comorbidities										
Neutropenia	23/639 (3.6)	12/296 (4.1)	5/156 (3.2)	1/20 (5.0)	4/52 (7.7)	0/25 (0.0)	0/22 (0.0)	1/68 (1.5)	10/266 (3.8)	.48
Fever	338/639 (52.9)	146/296 (49.3)	82/156 (52.6)	10/20 (50.0)	31/52 (59.6)	14/25 (56.0)	14/22 (63.6)	41/68 (60.3)	145/266 (54.5)	.53
Organ rejection	242/635 (38.1)	114/293 (38.9)	55/156 (35.3)	7/20 (35.0)	20/52 (38.5)	10/25 (40.0)	5/21 (23.8)	31/68 (45.6)	96/266 (36.1)	.65
CMV[2]	43/639 (6.7)	14/296 (4.7)	9/156 (5.8)	3/20 (15.0)	3/52 (5.8)	3/25 (12.0)	4/22 (18.2)	7/68 (10.3)	21/266 (7.9)	.08
Renal insufficiency[3]	287/639 (44.9)	133/296 (44.9)	73/156 (46.8)	6/20 (30.0)	22/52 (42.3)	12/25 (48.0)	11/22 (50.0)	30/68 (44.1)	121/266 (45.5)	.87
Hepatic insufficiency[3]	150/639 (23.5)	72/296 (24.3)	38/156 (24.4)	7/20 (35.0)	7/52 (13.5)	3/25 (12.0)	1/22 (4.5)	22/68 (32.4)	55/266 (20.7)	.03
Malnutrition[3]	187/639 (29.3)	92/296 (31.1)	45/156 (28.8)	3/20 (15.0)	13/52 (25.0)	3/25 (12.0)	4/22 (18.2)	27/68 (39.7)	66/266 (24.8)	.08
Diabetes[3]	299/639 (46.8)	143/296 (48.3)	71/156 (45.5)	6/20 (30.0)	21/52 (40.4)	7/25 (28.0)	9/22 (40.9)	42/68 (61.8)	111/266 (41.7)	.04
CHF	51/639 (8.0)	26/296 (8.8)	8/156 (5.1)	0/20 (0.0)	3/52 (5.8)	1/25 (4.0)	1/22 (4.5)	12/68 (17.6)	13/266 (4.9)	.03
Prednisone[1]	469/639 (73.4)	228/296 (77.0)	113/156 (72.4)	12/20 (60.0)	36/52 (69.2)	17/25 (68.0)	15/22 (68.2)	48/68 (70.6)	187/266 (70.3)	.5
MPS[1]	108/639 (16.9)	41/296 (13.9)	35/156 (22.4)	5/20 (25.0)	8/52 (15.4)	2/25 (8.0)	6/22 (27.3)	11/68 (16.2)	55/266 (20.7)	.15
Infection site										
Bloodstream	286/639 (44.8)	95/296 (32.1)	91/156 (58.3)	9/20 (45.0)	40/52 (76.9)	19/25 (76.0)	12/22 (54.5)	20/68 (29.4)	167/266 (62.8)	<.001
Abdominal	90/639 (14.1)	46/296 (15.5)	19/156 (12.2)	2/20 (10.0)	2/52 (3.8)	0/25 (0.0)	2/22 (9.1)	19/68 (27.9)	24/266 (9.0)	<.001
Pulmonary	36/639 (5.6)	26/296 (8.8)	6/156 (3.8)	0/20 (0.0)	1/52 (1.9)	3/25 (12.0)	0/22 (0.0)	0/68 (0.0)	10/266 (3.8)	.01

(Continues)

TABLE 1 (Continued)

Variable	All species N (%)	*C. albicans* 296 (46.3)	*C. glabrata* 156 (24.4)	*C. krusei* 20 (3.1)	*C. parapsilosis* 52 (8.1)	*C. tropicalis* 25 (3.9)	Other	Multiple 68 (10.6)	Non-*albicans*	*P*-value[1]
Disseminated	23/639 (3.6)	11/296 (3.7)	8/156 (5.1)	1/20 (5.0)	0/52 (0.0)	1/25 (4.0)	0/22 (0.0)	2/68 (2.9)	10/266 (3.8)	.67
CNS	4/639 (0.6)	3/296 (1.0)	0/156 (0.0)	1/20 (5.0)	0/52 (0.0)	0/25 (0.0)	0/22 (0.0)	0/68 (0.0)	1/266 (0.4)	.18
Antifungal therapy										
Triazole	421/639 (65.9)	226/296 (76.4)	83/156 (53.2)	7/20 (35.0)	34/52 (65.4)	17/25 (68.0)	12/22 (54.5)	42/68 (61.8)	148/266 (55.6)	<.001
Amphotericin B	182/639 (28.5)	73/296 (24.7)	52/156 (33.3)	7/20 (35.0)	16/52 (30.8)	8/25 (32.0)	6/22 (27.3)	20/68 (29.4)	87/266 (32.7)	.59
Echinocandin	229/639 (35.8)	59/296 (19.9)	85/156 (54.5)	10/20 (50.0)	22/52 (42.3)	12/25 (48.0)	6/22 (27.3)	35/68 (51.5)	131/266 (49.2)	<.001
Antifungal prophylaxis[1]										
Triazole	191/639 (29.9)	62/296 (20.9)	66/156 (42.3)	15/20 (75.0)	18/52 (34.6)	7/25 (28.0)	5/22 (22.7)	18/68 (26.5)	110/266 (41.4)	<.001
Amphotericin B	39/639 (6.1)	15/296 (5.1)	9/156 (5.8)	3/20 (15.0)	2/52 (3.8)	4/25 (16.0)	1/22 (4.5)	5/68 (7.4)	18/266 (6.8)	.21
Echinocandin	25/639 (3.9)	9/296 (3.0)	5/156 (3.2)	2/20 (10.0)	6/52 (11.5)	1/25 (4.0)	1/22 (4.5)	1/68 (1.5)	15/266 (5.6)	.06

P-value applies to comparison of variables across species. Non-*albicans* species is excluded from this comparison as it represents a sum of all the non-*albicans* species listed in the table.
[1]Preceding and at the time of invasive candidiasis diagnosis.
[2]CMV in tissue or viremia.
[3]Definitions in supplemental Data S1.
OTR, organ transplant recipient; SD, standard deviation; CMV, cytomegalovirus disease; CHF, congestive heart failure; MPS, methylprednisolone; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.

30 days) and 411 were diagnosed late. The mean patient age was 47.4 years and the majority of patients were Caucasian (82.2%). Several comorbidities were common in cases, including renal (287, 44.9%) and hepatic (150, 23.5%) insufficiency, malnutrition (29.3%), and diabetes (299, 46.8%). In addition, allograft rejection was present in 38% (242) of cases. Patients often received antifungal prophylaxis (nearly 40%) at the time of the diagnosis of IC, most with a triazole (fluconazole most frequent; triazole 29.9%, amphotericin B [AmB] formulation 6.1%, echinocandin 3.9%). For treatment of IC, almost 66% of patients received a triazole, compared with an AmB formulation (28%) or an echinocandin (36%).

3.2 | Characteristics of IC among *Candida* species

Survival by *Candida* species varied as shown in Figure 1. The 90-day mortality by species was 22.6% for *C. albicans*, 27.7% for *C. glabrata*, 31.5% for *Candida krusei*, 35.2% for *C. parapsilosis*, and highest for *Candida tropicalis* (44%). Epidemiological features in patients with *C. albicans* (n=296) were contrasted with those who had infection with the second most common species, *C. glabrata* (n=156). Logistic regression identified both female gender and black race as independent demographic predictors of invasive *C. glabrata* infection (Table 2). Triazole antifungal use prior to infection was linked to *C. glabrata* infection.[18–20] The patient age associated with *C. glabrata* in this cohort was 49 years.[21–24] An additional treatment variable associated with *C. glabrata* infection was use of methyprednisolone (MPS).

We also compared patients with *C. albicans* (n=296) to those with the aggregate non-*albicans* species population (n=258). Independent risk factors for IC caused by non-*albicans* species were similar to those for *C. glabrata* alone and included black race, female gender, triazole antifungal prophylaxis, kidney transplant over other types of organ transplant, and MPS use. Distinct risk factors associated with *C. parapsilosis* included younger age (40.3 years, IQR 28.0-58.7). In addition, antifungal prophylaxis with an echinocandin drug was more common in the patients with *C. parapsilosis* breakthrough infections. Among the non-*albicans* species, late disease onset (>90 days) was also most common for *C. parapsilosis* infection.

3.3 | Characteristics of IC among transplant organ types

In total, 48 heart, 55 lung, 38 pancreas, 224 kidney, 261 liver, and 58 kidney-pancreas OTRs were diagnosed with IC. The aggregate mortality associated with IC was 26.5%, but was greatest in the heart, lung, and liver transplant cohorts (heart 25.5%, lung 36.4%, liver 30.9%, pancreas 13.2%, kidney 22.3%, kidney-pancreas 15.5%). Allograft rejection was common in the aggregate IC population, but was most common in heart transplant recipients (52.1% vs [32.4%-41.4%]). Use of MPS was also more common in the heart transplant group (33.3% vs [13.8%-18.2%]).

Bloodstream infection was the most common manifestation across the transplant organ types. Intra-abdominal infection was the next most frequent infection site and was associated with allografts below

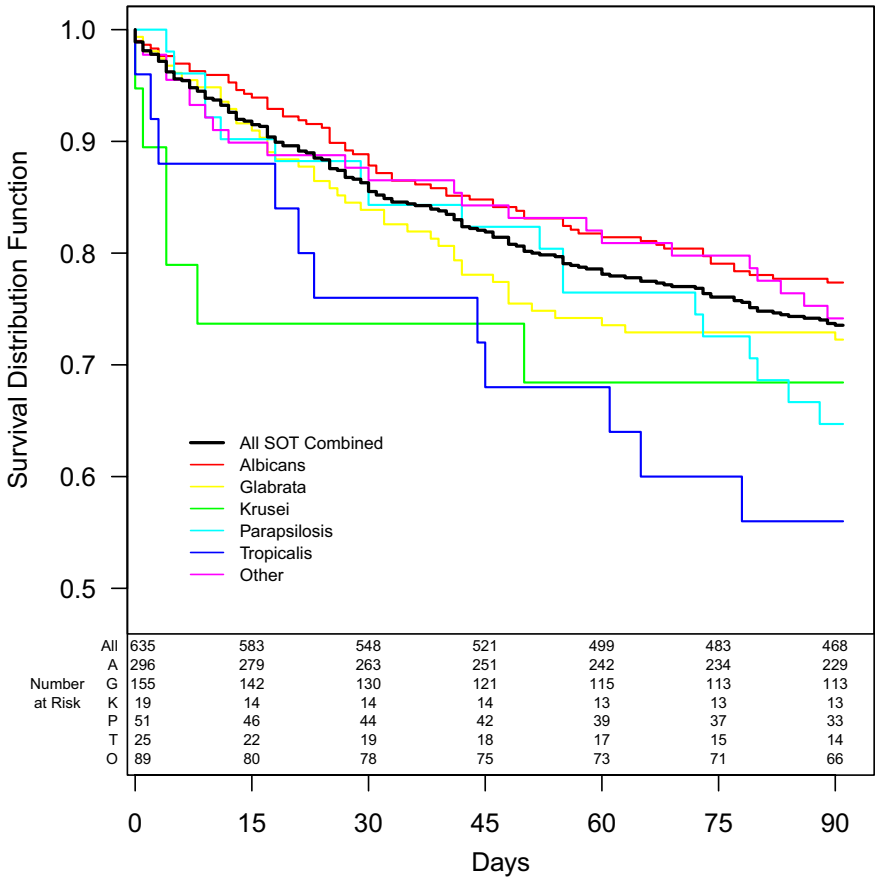

FIGURE 1 Kaplan–Meier probability of survival in solid organ transplant (SOT) recipients according to *Candida* species

TABLE 2 Multivariate analysis of risk factors for infection with select *Candida* species

Variable	Odds ratio	Lower	Upper	*P*-value
C. albicans vs non-*albicans Candida*				
Black	0.59	0.35	0.98	.040
Female	0.65	0.44	0.96	.032
Methyprednisolone	0.57	0.33	0.97	.039
Pulmonary site	3.22	1.26	8.24	.015
CHF	2.14	0.92	5.00	.078
Kidney	0.59	0.39	0.90	.015
Pancreatitis disease	2.44	1.02	5.81	.045
Triazole therapy	0.37	0.24	0.57	<.001
C. albicans vs *C. glabrata*				
Black	0.57	0.31	1.03	.063
Female	0.46	0.29	0.72	.001
Age	0.98	0.97	1.00	.028
Methyprednisolone	0.42	0.24	0.74	.003
Triazole prophylaxis	0.39	0.24	0.62	<.001
Candida parapsilosis vs non-*parapsilosis Candida*				
Age	0.98	0.96	0.99	.011
Early disease	0.43	0.19	0.95	.037
Echinocandin therapy	4.06	1.47	11.18	.007

CHF, congestive heart failure.

the diaphragm (pancreas 26.3%, liver 20.7%, kidney-pancreas 19%). Antifungal prophylaxis was common among all OTRs with IC (39%); however, this practice was most common for the heart and lung allograft recipients (heart 64.8%, lung 70.9% vs pancreas 28.9%, kidney 29.9%, liver 44.8%, and kidney-pancreas 51.7%). Among patients who developed IC, antifungal prophylaxis with a triazole was most commonly administered to kidney-pancreas transplant (26/58 44.8%) and lung transplant recipients (24/55 43.6%). AmB and echinocandin prophylaxis were much less common in all OTRs. Use of these agents was observed predominantly in the liver transplant cohort (amphotericin 33/261 12.6% and echinocandin 14/261 5.4%).

Triazoles were the most common antifungal drugs used for treatment of IC. This treatment was particularly frequent in pancreas (28/38; 73.7%) and kidney transplant recipients (158/224; 70.5%). Additional characteristics in the different transplant types are shown in Table S1.

3.4 | Predictors of mortality in patients with IC

Ninety-day mortality for all patients was 168/635 (26.5%). Kaplan–Meier estimate of 30-day survival was 85.5%. Survival was statistically different among *Candida* species (Figure 1). The mortality for non-*albicans* group was higher than for *C. albicans* (non-*albicans* [80/255] 31.4% vs *C. albicans* [67/296] 22.6%, *P*=.02). Much of this difference was driven by *C. glabrata*. However, mortality associated with *C. parapsilosis* and *C. tropicalis* infection was also high (35.2% and 44% respectively). Independent predictors of mortality in OTRs with IC across all *Candida* species included renal impairment, congestive heart failure, lung transplant, and treatment with an AmB formulation (Table 3). Prednisone use and IC in the early transplant period (30 days) were associated with reduced risk of mortality.

We performed several subgroup analyses to explore unique outcome factors based on *Candida* species, organ transplant type, and infection site (Table 4). The majority of elements correlating with outcome were similar among the organism, host, and disease state groups. Organ dysfunction, infection dissemination, and allograft rejection were shared features among those patients who died. A unique association among the subgroups included the relative protection for patients receiving echinocandins in the setting of *C. glabrata* infection (OR 0.45, 95% CI 0.17-0.97). Conversely, a trend was seen toward reduced efficacy with this antifungal drug class for *C. parapsilosis* infection (61.1% in those that died vs 30.3% in survivors, *P*=.03). Among the renal transplant cohort, the use of AmB was linked to poor outcome (42% in those who died vs other 21.8% in survivors, *P*<.001).

4 | DISCUSSION

Infection with *Candida* species was the most common invasive fungal infection among the TRANSNET solid organ transplant population.[14] The present report included surveillance of >15% of organ transplants occurring in the US during the study period, and is among the largest prospective investigations reporting the epidemiology and outcomes of IC in solid OTRs. The results document the importance of IC for this growing patient population. A common theme includes identification of a high prevalence of comorbidities in this IC population, underscoring the complexity of the patients with IC. Almost 50% of OTRs had renal insufficiency, one-fourth had hepatic dysfunction, nearly 50% had diabetes, and 30% had malnutrition. Nearly 40% experienced episodes of rejection, which may have contributed to the prevalence of organ dysfunction either caused by rejection or anti-rejection therapy. Furthermore, a large percentage of patients had received antifungal prophylaxis prior to development of IC.

Against this backdrop, we found that, similar to other epidemiologic studies of IC, *C. albicans* remained the most frequent pathogen. However, >10% of cases included infection with 2 or more *Candida* species. The frequency in the present study is more than twice that previously reported.[21,25–28] Similar to prior reports, this epidemiologic feature did not impact outcome in this cohort. Over the last 2 decades, the proportion of non-*albicans Candida* species causing IC has steadily increased.[9,26,29–33] The second most common pathogen in the present study was *C. glabrata*.[34–36] The relevance of this increase in non-*albicans* infections relates to potential for reduced treatment efficacy with certain antifungals owing to differences in susceptibility, in particular, the reduced susceptibility of *C. glabrata* and *C. parapsilosis* to triazole and echinocandin antifungal drugs respectively.[37–40] Antifungal susceptibility testing of available isolates demonstrated elevated minimum inhibitory concentrations for these species and drug combinations.[40] Interestingly, outcome for patients infected with non-*albicans* species in this transplant cohort was worse than for those with disease caused by *C. albicans*.

It is notable that we found prophylactic use of drugs from the triazole and echinocandin classes was common for *C. glabrata* and *C. parapsilosis* infections and was statistically associated with poorer outcome for these 2 species. The apparent superiority of the echinocandin class for treatment of IC, including infection caused by *C. glabrata*, has been observed in recent analysis.[41] Reduced efficacy for this class against less susceptible species, such as *C. parapsilosis*, has not been evident in clinical trials.[38,42,43] It is possible that the advanced degree of immunosuppression in this cohort, as suggested by the high rate of both multiorgan failure and allograft rejection, raised the therapeutic hurdle for this pathogen, which is traditionally considered among the least virulent. Indeed, the mortality rate in the transplant population infected with *C. parapsilosis* was unusually high compared to previous reports.[44,45] However, the relatively small number of patients with *C. parapsilosis* in this series precludes drawing firm therapeutic conclusions.

Another unique observation is the relatively young age of patients with *C. glabrata* infections (<50 years). Other large surveillance studies have reported increased *C. glabrata* risk beyond the fifth decade.[20,46,47] This finding may be in part a result of a relatively low percentage of transplant recipients above the fifth decade in this cohort (50.2% age >50 at time of transplant). Two additional unique *C. glabrata* risk factors of note in the current investigation include the relevance of female gender and black race. A similar race observation has been described for cryptococcal infections in the setting of organ transplantation.[48] However, the mechanistic basis for this epidemiologic finding remains unclear. We also observed a correlation between the use of

TABLE 3 Multivariate analysis of risk factors for mortality in OTRs with invasive candidiasis

Variable	Odds ratio	Lower	Upper	*P*-value
Candida species subgroup				
All species				
Liver transplant	1.63	0.96	2.76	.071
Renal insufficiency	2.31	1.46	3.66	<.001
Hepatic insufficiency	1.68	0.97	2.91	.066
CHF	3.54	1.61	7.81	.002
Pulmonary site	2.88	1.35	6.16	.006
Prednisone	0.39	0.25	0.63	<.001
Amphotericin B	1.99	1.24	3.2	.004
Early disease	0.51	0.3	0.84	.009
C. albicans				
Heart transplant	0.13	0.03	0.55	.006
Renal insufficiency	3.77	1.82	7.8	<.001
CHF	3.49	1.2	10.11	.022
Pulmonary site	2.88	0.86	9.66	.088
Disseminated site	8.66	1.74	43.01	.008
Prednisone	0.37	0.17	0.8	.012
Methyprednisolone	2.61	0.98	6.93	.054
Amphotericin B	2.85	1.31	6.22	.009
Echinocandin	3.25	1.4	7.58	.006
Early disease	0.36	0.15	0.85	.021
C. glabrata				
Age	1.05	1.02	1.09	.005
Pancreas transplant	9.84	1.46	66.26	.019
CHF	25.06	2.71	232.13	.005
Pulmonary site	5.17	0.68	39.49	.113
Prednisone	0.45	0.18	1.15	.094
Echinocandin	0.4	0.17	0.97	.042
Non-*albicans Candida*				
Heart	3.86	1.14	13.05	.03
Hepatic insufficiency	3.25	1.6	6.58	.001
CHF	9.02	1.67	48.57	.011
Pulmonary site	5.01	1.76	14.28	.003
Prednisone	0.48	0.25	0.93	.029
Early disease	0.54	0.27	1.09	.084
Transplant organ subgroups				
Kidney				
Hepatic insufficiency	17.28	4.42	67.53	<.001
CHF	6.29	1.89	20.93	.003
Renal insufficiency	3.63	1.39	9.44	.008
Prednisone	0.2	0.07	0.57	.003
Amphotericin	5.47	1.89	15.86	.002
Echinocandin	5.91	0.74	47.14	.093
Liver				
Renal insufficiency	3.12	1.54	6.32	.002
CMV	13.96	3.2	60.88	<.001
COPD	0.24	0.07	0.84	.026
Disseminated site	4.3	0.92	20.06	.063
Prednisone	0.27	0.13	0.6	.001
Methyprednisolone	0.28	0.09	0.89	.032
Early disease	0.39	0.18	0.86	.02
Candidemia subgroup				
Renal insufficiency	2.24	1.39	3.61	<.001
CHF	3.11	1.38	7.02	.006
Prednisone	0.41	0.25	0.68	<.001
Amphotericin	2.63	1.59	4.37	<.001
Echinocandin	2.01	1.22	3.3	.006
Early disease	0.46	0.27	0.8	.006

OTR, organ transplant recipient; CHF, congestive heart failure; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease.

MPS and non-*albicans Candida* infections, especially those caused by *C. glabrata*. We hypothesize that the use of this higher potency corticosteroid is a marker of organ rejection therapy reflecting enhanced immunosuppression. This observation is congruent with prior studies that link high mortality and *C. tropicalis* infection among patients with hematologic malignancies.[49–51] We did not identify unique transplant variables to explain this observation.

Candidemia was the commonest microbiologic manifestation of IC in this study. The second most common site was intra-abdominal, and not surprisingly, the majority of the cases occurred in abdominal cavity allografts.[52–54] Advanced disease, as marked by categorization as disseminated or organ disease other than abdominal was observed in >10% of patients. This rate of multi-organ involvement is comparable with reports of IC in the non-transplant population.[7,12,52,53] The impact of the pulmonary infection site on outcome is intriguing, but the relevance unclear. We speculate this could be an indication of dissemination or simply a high burden of *Candida*, as suggested in prior colonization studies.

Examination of antifungal choice for prophylaxis and therapy in the current population revealed a use pattern consistent with prior surveys.[12,21,55,56] Prophylaxis was dominated by the triazole class, predominantly fluconazole. Definitive treatment represented a mixed approach, and included a high percentage of echinocandins and comparatively little use of polyenes, probably owing to the differential risk for nephrotoxicity. Triazole prophylaxis in this cohort was successful in the prevention of IC by *C. albicans*, as previously reported.[56–59] However, the rate of breakthrough IC cases in this cohort was striking. Analyses demonstrated that many emergent infections were caused by species with higher minimum inhibitory concentrations to antifungal compounds.[42] In the setting of triazole prophylaxis, infection with

TABLE 4 Characteristics of OTRs with invasive candidiasis based upon transplant organ

Variable	Heart	Lung	Pancreas	Kidney	Liver	Kidney-pancreas
Demographics						
Age, mean±SD	52.8±19.3	48.2±15.7	44.5±7.5	48.1±12.9	46.9±17.1	42.6±9.1
Male	35/48 (72.9)	22/54 (40.7)	19/37 (51.4)	112/222 (50.5)	164/259 (63.3)	30/58 (51.7)
Female	13/48 (27.1)	32/54 (59.3)	18/37 (48.6)	110/222 (49.5)	95/259 (36.7)	28/58 (48.3)
Race						
Caucasian	39 (83.0)	43 (78.2)	37 (97.4)	167 (74.6)	204 (78.8)	48 (82.8)
Black	3 (6.4)	7 (12.7)	0 (0.0)	43 (19.2)	23 (8.9)	7 (12.1)
Other	5 (10.6)	5 (9.1)	1 (2.6)	14 (6.2)	32 (12.4)	3 (5.2)
Comorbidities						
Neutropenia	1/48 (2.1)	1/55 (1.8)	2/38 (5.3)	7/224 (3.1)	12/261 (4.6)	2/58 (3.4)
Fever	20/48 (41.7)	19/55 (34.5)	26/38 (68.4)	115/224 (51.3)	148/261 (56.7)	34/58 (58.6)
Organ rejection	25/48 (52.1)	22/55 (40.0)	12/37 (32.4)	87/224 (38.8)	88/260 (33.8)	24/58 (41.4)
CMV	4/48 (8.3)	4/55 (7.3)	2/38 (5.3)	12/224 (5.4)	20/261 (7.7)	3/58 (5.2)
Renal insufficiency	33/48 (68.8)	23/55 (41.8)	8/38 (21.1)	106/224 (47.3)	116/261 (44.4)	22/58 (37.9)
Hepatic insufficiency	6/48 (12.5)	2/55 (3.6)	1/38 (2.6)	29/224 (12.9)	111/261 (42.5)	6/58 (10.3)
Malnutrition	4/48 (8.3)	10/55 (18.2)	6/38 (15.8)	67/224 (29.9)	95/261 (36.4)	19/58 (32.8)
Diabetes	28/48 (58.3)	18/55 (32.7)	12/38 (31.6)	108/224 (48.2)	130/261 (49.8)	26/58 (44.8)
COPD	3/48 (6.2)	13/55 (23.6)	0/38 (0.0)	16/224 (7.1)	29/261 (11.1)	3/58 (5.2)
CHF	9/48 (18.8)	3/55 (5.5)	2/38 (5.3)	25/224 (11.2)	12/261 (4.6)	5/58 (8.6)
Autoimmune	3/48 (6.2)	6/55 (10.9)	0/38 (0.0)	19/224 (8.5)	15/261 (5.7)	2/58 (3.4)
Pancreatitis	2/48 (4.2)	0/55 (0.0)	2/38 (5.3)	30/224 (13.4)	11/261 (4.2)	11/58 (19.0)
HIV/AIDS	0/48 (0.0)	0/55 (0.0)	0/38 (0.0)	2/224 (0.9)	0/261 (0.0)	0/58 (0.0)
Prednisone	31/48 (64.6)	45/55 (81.8)	26/38 (68.4)	178/224 (79.5)	180/261 (69.0)	43/58 (74.1)
MPS	16/48 (33.3)	10/55 (18.2)	6/38 (15.8)	33/224 (14.7)	42/261 (16.1)	8/58 (13.8)
Candida species						
C. albicans	25 (53.2)	30 (54.5)	18 (47.4)	95 (42.4)	124 (47.9)	27 (46.6)
C. glabrata	9 (19.1)	9 (16.4)	13 (34.2)	62 (27.7)	57 (22.0)	18 (31.0)
C. krusei	2 (4.3)	0 (0.0)	1 (2.6)	6 (2.7)	9 (3.5)	1 (1.7)
C. parapsilosis	4 (8.5)	6 (10.9)	3 (7.9)	22 (9.8)	15 (5.8)	3 (5.2)
C. tropicalis	1 (2.1)	6 (10.9)	0 (0.0)	7 (3.1)	10 (3.9)	1 (1.7)
C. lusitaniae	1 (2.1)	0 (0.0)	0 (0.0)	3 (1.3)	1 (0.4)	0 (0.0)
Multiple	3 (6.4)	3 (5.5)	3 (7.9)	21 (9.4)	38 (14.7)	6 (10.3)
Other	1 (2.1)	0 (0.0)	0 (0.0)	3 (1.3)	4 (1.5)	1 (1.7)
Unspecified	1 (2.1)	1 (1.8)	0 (0.0)	5 (2.2)	1 (0.4)	1 (1.7)
Infection site						
Bloodstream	31/48 (64.6)	29/55 (52.7)	12/38 (31.6)	99/224 (44.2)	107/261 (41.0)	15/58 (25.9)
Abdominal	0/48 (0.0)	0/55 (00.0)	10/38 (26.3)	26/224 (11.6)	54/261 (20.7)	11/58 (19.0)
Pulmonary	4/48 (8.3)	17/55 (30.9)	1/38 (2.6)	3/224 (1.3)	9/261 (3.4)	1/58 (1.7)
Disseminated	3/48 (6.2)	0/55 (0.0)	1/38 (2.6)	9/224 (4.0)	10/261 (3.8)	2/58 (3.4)
CNS	0/48 (0.0)	0/55 (0.0)	0/38 (0.0)	3/224 (1.3)	1/261 (0.4)	0/58 (0.0)
Antifungal therapy[1]						
Triazole	31/48 (64.6)	38/55 (69.1)	28/38 (73.7)	158/224 (70.5)	158/261 (60.5)	39/58 (67.2)
Amphotericin	14/48 (29.2)	15/55 (27.3)	9/38 (23.7)	59/224 (26.3)	82/261 (31.4)	17/58 (29.3)
Echinocandin	13/48 (27.1)	10/55 (18.2)	14/38 (36.8)	85/224 (37.9)	102/261 (39.1)	24/58 (41.4)

(Continues)

TABLE 4 (Continued)

Variable	Heart	Lung	Pancreas	Kidney	Liver	Kidney-pancreas
Antifungal prophylaxis						
Triazole	19/48 (39.6)	24/55 (43.6)	11/38 (28.9)	58/224 (25.9)	70/261 (26.8)	26/58 (44.8)
Amphotericin	2/48 (4.2)	12/55 (21.8)	0/38 (0.0)	2/224 (0.9)	33/261 (12.6)	1/58 (1.7)
Echinocandin	1/48 (2.1)	3/55 (5.5)	0/38 (0.0)	7/224 (3.1)	14/261 (5.4)	3/58 (5.2)

[1]Includes sequential or combination therapy.

OTR, organ transplant recipient; SD, standard deviation; CMV, cytomegalovirus, COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; MPS, methylprednisolone; CNS, central nervous system.

C. glabrata was common. This observation is congruent with previously reported prophylaxis studies.[18] Interestingly, we also found an association between echinocandin prophylaxis and infection with *C. parapsilosis* (6/52, 11.5%), and this finding is consistent with the reduced efficacy described in the setting of definitive therapy described above.

A number of comorbidities were strongly related to poor outcomes. Neutropenia, heart failure, and renal and hepatic dysfunction each conferred a negative impact on outcome. Interestingly, we found a disparate impact for 2 corticosteroid formulations, prednisone and MPS. As noted above, we theorize that use of MPS is a marker of rejection and this likely translates into a risk for poor outcome. Conversely, use of prednisone may suggest stable allograft function and may explain the observed "protective" nature of this therapy. Early disease was also predictive of a favorable outcome. We theorize that this improvement may be a result of earlier diagnosis linked to enhanced vigilance in the early post-transplant period.

The results of this survey both confirm and extend our understanding of the features of IC in solid OTRs. We identified a hierarchy of risk for disease and outcome based on transplant type, underlying disease, and comorbid conditions. We did not identify directly modifiable factors, other than an emphasis on the importance of drug selection for certain *Candida* species, which is intuitive based upon fairly predictable antifungal drug susceptibility. Current evidence suggests that echinocandins are the optimal empiric antifungal drug choice for IC.[43] In the current study, this benefit is less clear for infection caused by *C. parapsilosis*, but numbers are small. The absence of other readily identifiable factors under the direct control of clinicians underscores the importance of a high index of suspicion in this complex patient population. In particular, the presence of organ dysfunction and rejection should prompt surveillance for this infectious complication. Furthermore, these observations highlight the need for improved fungal diagnostics and more effective antifungal compounds.

The TRANSNET database is comprehensive, but it has several limitations. Baseline and longitudinal laboratory data were minimal and specific information about drug exposure was incomplete. For example, information regarding antifungal, antiviral, and antibacterial prophylaxis was limited, as were data pertaining to vascular catheter management, immunosuppressive regimens, and institution-specific practices and protocols. It is possible that information regarding catheters may have shed light on the relatively high mortality linked to *C. parapsilosis* infection. Moreover, the dataset does not include data on disease severity and transplant incompatibility characteristics. These important covariates should be explored more fully in future studies. In addition, the period of data collection ended in 2006, thus practice changes may have occurred that limit extrapolation of findings. For example, echinocandins have emerged as the preferred therapy for treatment of IC over AmB and triazoles. Immunosuppressive and antifungal prophylaxis regimens also continue to evolve. Finally, this analysis is based on all-cause mortality, as attribution to IC as a contributing cause to mortality is difficult, and generally reflects investigator opinion. Despite these limitations, this analysis from a large and comprehensive database provides important insights into factors that are associated with mortality among OTRs who develop IC, and these data may be useful in developing strategies for prevention and treatment of this important post-transplantation complication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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