Voriconazole Exposure and Risk of Cutaneous Squamous Cell Carcinoma, *Aspergillus* Colonization, Invasive Aspergillosis and Death in Lung Transplant Recipients

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Voriconazole is a triazole antifungal used to prevent and treat invasive fungal infections after lung transplantation, but it has been associated with an increased risk of developing cutaneous squamous cell carcinoma (SCC). Despite widespread use, there are no clear guidelines for optimal prophylactic regimens that balance the competing risks and benefits. We conducted a retrospective cohort study of all lung transplant recipients at the University of California, San Francisco, who were transplanted between October 1991 and December 2012 (n = 455) to investigate whether voriconazole exposure affected development of SCC, *Aspergillus* colonization, invasive aspergillosis and all-cause mortality. Voriconazole exposure was associated with a 73% increased risk of developing SCC (hazard ratio [HR] 1.73; 95% confidence interval [CI]: 1.04–2.88; p = 0.03), with each additional 30-day exposure at the standard dose increasing the risk by 3.0% (HR 1.03; 95% CI: 1.02–1.04; p < 0.001). Voriconazole exposure reduced risk of *Aspergillus* colonization by 50% (HR 0.50; 95% CI: 0.34–0.72; p < 0.001), but we were underpowered to detect risk reduction for invasive aspergillosis. Voriconazole exposure significantly reduced all-cause mortality among subjects who developed *Aspergillus* colonization (HR 0.34; 95% CI: 0.13–0.91; p = 0.03) but had no significant impact on those without colonization. Physicians should consider patient-specific factors that modify the potential risks and benefits of voriconazole for the care of lung transplant recipients.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; eHR, expanded hazard ratio; HR, unadjusted hazard ratio; LAS, Lung Allocation Score; OPTN, Organ Procurement and Transplantation Network; SCC, squamous cell carcinoma; SD, standard deviation; STAR, Standard Transplant Analysis and Research; UCSF, University of California, San Francisco

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Introduction

Skin cancer is the most common malignancy after solid organ transplantation. Notably, organ transplant recipients experience a >65-fold increased risk of developing cutaneous squamous cell carcinoma (SCC) compared with the general population (1). SCCs that develop in organ transplant recipients behave aggressively and can lead to a large number of cutaneous lesions, resulting in multiple debilitating surgeries and increased risk of death (2,3). Lung transplant recipients are particularly susceptible because of older age at transplant and more intensive immunosuppression (4–8).

Lung transplant recipients also have high rates of fungal infections after transplantation (15%–35%), which can result in significant morbidity and mortality (up to 78% for invasive infections) (9). Many lung transplant programs implement universal antifungal prophylaxis after transplant based on evidence that this approach may reduce incidence of invasive fungal infections and death (10). Targeted prophylaxis or treatment is also often reinstituted in patients with evidence of fungal colonization and/or in those requiring increased immunosuppression used to treat acute allograft rejection. Voriconazole is a broad-spectrum triazole antifungal first approved in 2002 for the treatment and prevention of invasive fungal infections. In a recent worldwide survey (11), voriconazole-based antifungal prophylaxis regimens were the most commonly used in lung transplant recipients. This is likely because of the
drug’s relative ease of administration and effectiveness compared with other therapeutics (12).

Retrospective cohort and case–control studies have demonstrated that voriconazole increases the risk of developing SCC in lung transplant recipients (13–15). Our group recently showed that any voriconazole exposure is associated with a 2.6-fold increased risk of SCC in lung transplant recipients and that the risk is dose dependent (16). Although the exact mechanism of carcinogenesis is not well understood, it may result from drug-associated phototoxicity (17,18).

No clear guidelines exist for the optimal dose and duration of voriconazole prophylaxis in lung transplant recipients. Importantly, prior studies evaluating voriconazole exposure and risk for SCC have not balanced this finding against the drug’s potential for reducing invasive fungal infections and mortality. To evaluate the relative risks and benefits of voriconazole in lung transplant recipients, we conducted an expanded 21-year, single-center, retrospective cohort study.

Materials and Methods

Cohort population
To investigate the effect of voriconazole exposure on the risk of SCC, Aspergillus colonization, invasive aspergillosis and all-cause mortality after lung transplantation, we performed a single-center retrospective cohort study of all patients who underwent single-lung, double-lung or heart–lung transplantation at the University of California, San Francisco (UCSF) from October 23, 1991, to December 27, 2012 (n = 455). This study was approved by the UCSF Committee on Human Research and was performed in compliance with the Declaration of Helsinki.

Measurement of drug exposure
At UCSF, all lung transplant recipients receive universal antifungal prophylaxis for 3 months following transplantation starting on postoperative day 3. Posttransplant prophylaxis was extended or therapy was reinstituted at the discretion of the treating physician for treatment of fungal colonization of the respiratory tract or when immunosuppression was increased as a result of an acute rejection episode. Most invasive infections were treated for 6–8 weeks. Between 1991 and 2002, inhaled amphotericin B was used by protocol for both prophylaxis against and treatment for Aspergillus colonization and invasive fungal infections. In 2002, voriconazole was introduced into the care of lung transplant recipients at UCSF for treatment of Aspergillus colonization and invasive fungal infections. In 2005, voriconazole replaced inhaled amphotericin B as the first-line medication for prophylaxis.

Drug exposure information for outpatient administration of voriconazole, inhaled amphotericin B, and posaconazole was obtained using medical record review, as described previously (16). For the purposes of this study, we standardized postoperative day 3 after lung transplant as our index (start) date for obtaining drug dosing. Patients who underwent retransplantation (n = 14) were assessed from the index date of their first transplant.

Covariates
We assessed risk factors associated with development of SCC, invasive aspergillosis and death. We acquired all demographic data from the Organ Procurement and Transplantation Network (OPTN) registry (Standard Transplant Analysis and Research [STAR] dataset file 020910–16) and medical record review. Covariates include sex, race/ethnicity, age at transplant, Lung Allocation Score (LAS) diagnostic category (19), type of transplant (single-lung, double-lung, or heart–lung transplantation), and year of transplant (era effect). Smoking history, a known risk factor for SCC (20), was missing for 160 (37.9%) patients and was not included. History of cytomegalovirus disease, a risk factor for invasive aspergillosis in organ transplant recipients (21), was not evaluated because of low cumulative incidence in our cohort (n = 5; 1.1%). We believe this low incidence is related to the fact that all lung transplant recipients at UCSF receive lifelong universal prophylaxis with valganciclovir (22).

Primary outcomes
We screened all medical records for diagnosis of SCC by a pathology or dermatopathology report with an International Classification of Diseases, 9th revision (ICD-9) code of 173.x or 232.x. Because these codes capture any nonmelanoma skin cancer, additional review was used to adjudicate whether these codes referred to SCC based on a line diagnosis of SCC, SCC in situ, Bowen’s disease, or keratoacanthoma. Skin cancer outcome data was missing for 7 of 455 (1.5%) patients, and they were excluded from outcome-specific analysis.

Invasive aspergillosis diagnosis was identified by two methods. First, medical records were reviewed for appropriate ICD-9 diagnostic codes (117.3 and 484.6) for invasive aspergillosis. Second, to ensure completeness, hospital and laboratory records of all lung transplants were reviewed to confirm a positive respiratory culture of Aspergillus. Potential cases were defined based on established European Organization for Research and Treatment of Cancer (EORTC) criteria for invasive fungal infection. Patients meeting the definition of probable or proven invasive aspergillosis were assigned a positive diagnosis (6). There were 13 of 455 (2.9%) patients with missing or insufficient data on invasive aspergillosis, and these patients were excluded from outcome-specific analysis.

We also assessed Aspergillus colonization, defined as the date of positive culture of any Aspergillus species from routine tracheal aspirate or bronchoalveolar lavage in the absence of invasive disease. We acquired dates of death, if applicable, from the OPTN registry.

Statistical analysis
We used survival analysis to test whether voriconazole exposure affected development of SCC, Aspergillus colonization, invasive aspergillosis and all-cause mortality. Multivariate Cox proportional hazards regression models were built with modified Allen–Cady backward selection to calculate the relative hazard ratios for each outcome by voriconazole exposure. For each outcome, we developed two separate analytic models expressing voriconazole drug exposure as either a time-varying covariate of any or no voriconazole exposure or a time-varying covariate of cumulative-dose voriconazole exposure, as described previously (16). For the cumulative-dose models, a single unit of drug exposure was defined as 12 gm, equivalent to 1 month (30 days) of voriconazole exposure at the standard dose of 200 mg twice daily. In each model, subjects exited the study if they developed the primary outcome, died or were lost to follow-up or the study period ended.

Drug exposure data was either incomplete or missing for 68 of 455 (15.0%) cohort members. The participants with missing data were similar with respect to age, sex, race, LAS diagnostic category and type of transplant but were more likely to have received a transplant in earlier years, were less likely to develop SCC and were more likely to have died by the end of the study period compared with those with complete data. To address this...
potential bias, we generated inverse weights based on a logistic regression model of missingness for these variables (23,24).

For multivariate adjustment, sex, race, and age at transplant were kept a priori, given their known association with SCC (25). LAS diagnostic category and type of transplant were not significant in any outcome model, but year of transplant was significant in the all-cause mortality outcome model only. Consequently, for all outcome analyses, we calculated the relative hazard ratio by drug exposure using an unadjusted Cox regression model (unadjusted hazard ratio [HR]); a model adjusted for sex, race, and age at transplant (aHR); and an expanded model that included year of transplant (eHR). For the SCC outcome only, patients with a prior history of SCC before lung transplantation (n = 4) were excluded from multivariate analysis by left censoring. The proportional hazards assumption was tested and confirmed with the Schoenfeld test. The goodness of fit of the models was confirmed by comparing a plot of the Cox-Snell residuals with the Nelson–Aalen cumulative hazard function.

We also conducted additional analysis for both the invasive aspergillosis and all-cause mortality outcome models, stratifying patients by history of Aspergillus colonization status because we hypothesized that colonization status might modify the relationship between voriconazole exposure and these outcomes (26). For SCC analysis only, we also developed a cumulative-dose exposure model that included voriconazole, inhaled amphotericin B, and posaconazole exposure to test whether or not alternative medications used for antifungal prophylaxis in lung transplant recipients also affected development of SCC after lung transplantation (ie, confounding by indication).

Finally, we used Kaplan–Meier methods to generate unadjusted outcome-free survival plots for our primary outcomes, stratifying cohort participants by any or no voriconazole exposure. We also calculated the cumulative incidence of our primary outcomes by any or no voriconazole exposure at 1, 5 and 10 years after transplant, adjusting for age at transplant, sex, race and year of transplant. For both analyses, voriconazole exposure status was assessed at the time of study exit (development of primary outcome, death, loss to follow-up or end of study period) for each cohort participant to capture only exposure that occurred prior to development of the primary outcome.

Statistical analyses were conducted using Stata version 12 (StataCorp, College Station, TX) with two-sided α < 0.05.

Results

Our cohort (n = 455) included 98 single-lung, 347 double-lung, and 10 heart-lung transplant recipients at UCSF. Patients were predominately male (53.6%) and white (79.1%) and had a median age at transplant of 55.4 years (range: 14.9–74.4 years) (Table 1). Among participants with complete data on drug exposure, 327 of 387 (84.5%) were exposed to voriconazole, and 60 of 387 (15.5%) were never exposed before study exit; any exposure was included in models as a time-varying covariate. The mean duration of voriconazole exposure was 9.8 months (standard deviation [SD]: 13.3 months; range: 0–98.7 months). Participants who were exposed to voriconazole were more likely to have undergone lung transplant later during our study period (median year of transplant: 2008; range: 1994–2012) compared with those never exposed to voriconazole (median year of transplant: 1998; range 1991–2012).

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**Table 1: Cohort demographic characteristics**

| Characteristic | Lung Transplant Cohort (n = 455) |
|---------------|----------------------------------|
| Age at transplant, years | 52.4 ± 12.4 |
| Age <50 | 164 (36.0) |
| Age ≥ 50 | 291 (64.0) |
| Sex | |
| Male | 244 (53.6) |
| Female | 211 (46.4) |
| Race/ethnicity | |
| White, non-Hispanic | 360 (79.1) |
| Nonwhite | 95 (20.9) |
| Black | 26 (5.7) |
| Hispanic | 42 (9.2) |
| Asian | 20 (4.4) |
| American Indian/Alaskan Native | 3 (0.7) |
| Hawaiian/other | 3 (0.7) |
| Multiracial | 1 (0.2) |
| Lung transplant indication by diagnostic category | |
| Group A (chronic obstructive pulmonary disease) | 141 (31.0) |
| Group B (pulmonary hypertension) | 44 (9.7) |
| Group C (cystic fibrosis) | 48 (10.6) |
| Group D (pulmonary fibrosis) | 222 (48.8) |
| Type of Transplant | |
| Single Lung | 98 (21.5) |
| Bilateral Lung | 347 (76.3) |
| Heart-Lung | 10 (2.2) |
| Year of Transplant | 2005 (5.4) |

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During the study period, 86 of 448 (19.20%) patients developed at least one SCC, 119 of 455 (26.2%) developed posttransplant Aspergillus colonization, 76 of 442 (16.7%) developed invasive aspergillosis, and 208 of 455 (45.7%) died (Table S1).

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**Squamous cell carcinoma**

Lung transplant recipients who developed SCC (n = 86) had a mean duration of 13.2 months of prior voriconazole exposure at SCC diagnosis (SD: 13.9 months; range: 0–67.5 months). Any exposure to voriconazole was associated with a 73% increased risk of developing SCC (aHR 1.73; 95% confidence interval [CI]: 1.04–2.88; p = 0.03). This relationship was dose dependent with each additional 12-gm dose of exposure (equivalent to 200 mg twice daily for 30 days), increasing the risk by 3.0% (aHR 1.03; 95% CI: 1.02–1.04; p < 0.001). In our expanded model adjusting for year of transplantation, although the effect size remained the same, the association of any exposure was no longer statistically significant (eHR 1.71; 95% CI: 0.83–3.52; p = 0.15) (Table 2). Covariates associated with SCC in previous studies were also associated with SCC in our cohort. These included age ≥50 years at transplant (eHR 1.87; 95% CI: 1.27–2.75; p = 0.001), male sex.
in a combined “triple drug” model adjusting for the cumulative-dose exposure to voriconazole, inhaled amphotericin B and posaconazole, we found that only voriconazole (eHR 1.03; 95% CI: 1.02–1.04; p < 0.001)—and neither inhaled amphotericin B (eHR 1.00; 95% CI: 0.99–1.01; p = 0.75) nor posaconazole (eHR 0.99; 95% CI: 0.95–1.05; p = 0.81)—was associated with development of SCC.

Using unadjusted Kaplan–Meier methods, any exposure to voriconazole was associated with an absolute risk increase for SCC of 15% at 5 years and 7% at 10 years (Figure 1A). In our cumulative incidence models adjusted for age, sex, race and year of transplant, we found that voriconazole-exposed participants had an absolute risk increase for SCC of 9% at 5 years and 15% at 10 years after transplantation (Table 3).

**Aspergillus colonization and invasive aspergillosis**

Any exposure to voriconazole was associated with a 50% decreased risk of developing *Aspergillus* colonization after lung transplantation (eHR 0.50; 95% CI: 0.34–0.72; p < 0.001), but this relationship was not dose dependent (Table 2); however, when we restricted analysis to the first year after transplant, we found an 18% decreased risk of colonization for each 30 days of drug exposure (eHR 0.82; 95% CI: 0.70–0.96; p = 0.01). No covariates were significantly associated with risk of colonization (Table S2). In our adjusted cumulative incidence model, we found voriconazole exposure was associated with an absolute risk decrease for colonization of 19% at 5 years and 24% at 10 years after transplant (Table 3).

Both drug exposure models showed a trend toward drug-related reduction in the risk of developing invasive aspergillosis after transplantation, but neither relationship...
reached statistical significance (Table 2). Colonization status did not modify this relationship (Table S3), and no covariates were significantly associated with risk of invasive aspergillosis (Table S2). Using unadjusted Kaplan Meier methods, any exposure to voriconazole was associated with an absolute risk decrease for invasive aspergillosis of 5% at both 5 and 10 years (Figure 1D). In our adjusted cumulative incidence models, we found voriconazole exposure was associated with an absolute risk decrease for invasive aspergillosis of 2% at 1 year, 4% at 5 years and 6% at 10 years after transplant (Table 3).

### All-cause mortality

Any exposure to voriconazole did not significantly affect all-cause mortality (eHR 1.32; 95% CI: 0.87–1.99; p = 0.19) in our overall cohort. Factors that were associated with all-cause mortality included white race (eHR 1.52; 95% CI: 1.05–2.21; p = 0.03) and year of transplant (eHR 1.99; 95% CI: 0.87–0.95; p < 0.001) (Table S2). Nonetheless, we found that Aspergillus colonization status modified the relationship between voriconazole exposure and mortality in stratified analysis. Voriconazole exposure reduced mortality risk by 66% among subjects colonized with Aspergillus (eHR 0.34; 95% CI: 0.13–0.91; p = 0.03) but had no significant impact on those without evidence of colonization (eHR 1.49; 95% CI: 0.90–2.48; p = 0.12) (Table S3). In our cumulative-dose model, we found a 2% increased mortality risk for each 30-day exposure to voriconazole (eHR 1.02, 95% CI: 1.01–1.03; p < 0.001) in the overall cohort (Table 2). In stratified analysis, however, we found this increased mortality risk was restricted to

### Table 2: Unadjusted, adjusted, and expanded hazard ratios for primary and secondary outcomes by voriconazole exposure

| Outcome                            | HR (95% CI) | p value | aHRa (95% CI) | p value | eHRb (95% CI) | p value |
|------------------------------------|-------------|---------|---------------|---------|---------------|---------|
| Squamous cell carcinoma            |             |         |               |         |               |         |
| Any exposure                       | 1.91 (1.11–3.27) | 0.02    | 1.73 (1.04–2.88) | 0.03    | 1.71 (0.83–3.52) | 0.15    |
| Cumulative-dose exposured          | 1.02 (1.01–1.03) | 0.001   | 1.03 (1.02–1.04) | <0.001  | 1.03 (1.02–1.04) | <0.001  |
| Aspergillus colonization            |             |         |               |         |               |         |
| Any exposure                       | 0.52 (0.39–0.71) | <0.001  | 0.52 (0.39–0.70) | <0.001  | 0.50 (0.34–0.72) | <0.001  |
| Cumulative-dose exposured          | 0.99 (0.96–1.01) | 0.34    | 0.99 (0.96–1.01) | 0.37    | 1.00 (0.97–1.02) | 0.71    |
| Invasive aspergillosis             |             |         |               |         |               |         |
| Any exposure                       | 0.76 (0.43–1.35) | 0.35    | 0.79 (0.45–1.37) | 0.40    | 0.78 (0.40–1.49) | 0.45    |
| Cumulative-dose exposured          | 0.98 (0.95–1.02) | 0.32    | 0.98 (0.95–1.02) | 0.33    | 0.98 (0.95–1.02) | 0.38    |
| All-cause mortality                |             |         |               |         |               |         |
| Any exposure                       | 0.66 (0.47–0.93) | 0.02    | 0.64 (0.45–0.90) | 0.01    | 1.32 (0.87–1.99) | 0.19    |
| Cumulative-dose exposured          | 1.01 (1.00–1.02) | 0.04    | 1.01 (1.01–1.02) | 0.05    | 1.02 (1.01–1.03) | <0.001  |

aHR, adjusted hazard ratio; CI, confidence interval; eHR, expanded hazard ratio; HR, unadjusted hazard ratio.

cAdjusted for sex, race (white vs. nonwhite) and age at transplant.

dAdjusted for sex, race (white vs nonwhite), age at transplant, and year of transplant.

eVersus subjects never exposed to voriconazole.

fPer 12 gm of voriconazole exposure (equivalent to 200 mg twice daily for 30 days).

### Table 3: Adjusted cumulative incidence of primary outcomes by voriconazole exposure

| Years after transplant | Adjusted cumulative incidencea (%) | | | | |
|------------------------|-----------------------------------|---|---|---|
|                        | No voriconazole exposure | Any voriconazole exposure | Absolute risk difference (%) |
| Squamous cell carcinoma| 1 year 1 |1 |0 |
|                        | 5 years 15 |25 |+10 |
|                        | 10 years 28 |43 |+15 |
| Aspergillus colonization| 1 year 28 |15 |−13 |
|                        | 5 years 44 |25 |−19 |
|                        | 10 years 63 |39 |−24 |
| Invasive aspergillosis  | 1 year 10 |8 |−2 |
|                        | 5 years 22 |18 |−4 |
|                        | 10 years 27 |21 |−6 |
| All-cause mortality     | 1 year 7 |8 |+1 |
|                        | 5 years 39 |47 |+8 |
|                        | 10 years 58 |69 |+11 |

aAdjusted for age at transplant, sex, race, and year of transplant.

266 American Journal of Transplantation 2016; 16: 262–270

Mansh et al
participants without evidence of colonization (eHR 1.02; 95% CI: 1.01–1.04; p < 0.001). There was no dose relationship between voriconazole exposure and all-cause mortality among subjects with *Aspergillus* colonization (eHR 1.00; 95% CI: 0.98–1.03; p = 0.61) (Table S3).

Using unadjusted Kaplan–Meier methods, voriconazole exposure was associated with an absolute risk decrease for all-cause mortality of 14% at 5 years and 8% at 10 years (Figure 1B). In the adjusted cumulative incidence model, however, we found an absolute risk increase for mortality of 9% at 5 years and 10% at 10 years after transplant in the overall cohort (Table 3). In a sensitivity analysis, we found that the disparity between the results of our unadjusted Kaplan–Meier and multivariate adjusted cumulative incidence analyses was primarily due to adjustment for year of transplant.

**Discussion**

In this retrospective cohort study of 455 lung transplant recipients, we found that voriconazole exposure was associated with an increased risk of developing SCC but also was associated with a significantly reduced risk of developing *Aspergillus* colonization after lung transplantation and, among those that became colonizers, all-cause mortality. We found that voriconazole exposure after lung transplantation was associated with a 73% increased risk of SCC and that this relationship was dose dependent, with each additional 30-day exposure at the standard dose of 200 mg twice daily increasing the risk by 3%. These results are consistent with our previous cohort study, which demonstrated a 6% increased risk for each 60-day exposure (16). Although the relationship between any exposure to voriconazole and SCC became insignificant after controlling for year of transplant, the stability of the point estimates suggests this was most likely due to a degree of multicollinearity between year of transplant and any voriconazole exposure. We extended these previous findings with a larger and more statistically powered study to demonstrate that inhaled amphotericin B and posaconazole do not confer an increased risk of SCC in these patients. This finding is important because recent research suggests that these medications, including their newer formulations, may both be clinically efficacious (27) and cost-effective (28) for fungal prophylaxis in immunosuppressed patients and may potentially represent safer alternatives for patients with a high risk of SCC. Our findings also contradict the recent suggestion that the association between voriconazole and SCC is a result of confounding by indication (29). Finally, we validated patient-specific demographic factors that significantly increase SCC risk in lung transplant recipients, including male sex, older age at transplant and white race, which are similar to the general population (30,31).

For the first time, we also assessed the potential benefits of voriconazole exposure for reducing invasive fungal infections and all-cause mortality in the context of this risk. We found a statistically insignificant trend that voriconazole exposure reduced invasive aspergillosis, although the low incidence of this outcome in our cohort (79 of 442 patients; 16.47%) limited the power of our study to detect this difference. Voriconazole exposure provided a 50% decreased risk of developing *Aspergillus* colonization after transplantation, and that effect was dose dependent during the first year after transplant. These findings are particularly notable because posttransplant *Aspergillus* colonization has been associated with up to an 11-fold increased risk of developing invasive aspergillosis as well as a 2-fold increased risk of all-cause mortality, even among patients who never develop invasive aspergillosis (32–34).

Voriconazole exposure reduced mortality by 66% among those with *Aspergillus* colonization, possibly due to prevention of other sequelae of colonization, such as bronchiolitis obliterans syndrome (35,36), even in the absence of a statistically significant reduction of invasive aspergillosis. This relationship was not dose dependent, however, suggesting that prolonged voriconazole administration may not provide significant mortality benefit compared with shorter treatment durations in these patients.

 Patients without evidence of *Aspergillus* colonization appear to be particularly susceptible to an imbalance in the risks and benefits of voriconazole administration. In those without colonization, voriconazole conferred no risk reduction for either invasive aspergillosis or mortality. In fact, we found a 2% increased risk of mortality for each additional 30 days of exposure. An alternative possibility is that those receiving higher cumulative doses of voriconazole possessed additional risk factors for death that were not controlled for in our models, such as increased intensity of immunosuppression (37) or episodes of rejection (38). Prior studies have not reported this relationship, but it deserves further investigation (39).

Efficacy data concerning the benefits of voriconazole prophylaxis in lung transplant recipients remains limited. A recent systematic review and meta-analysis of universal antifungal prophylaxis in lung transplantation concluded that there is no definitive evidence that universal antifungal prophylaxis, including regimens that use voriconazole, significantly reduces incidence of invasive aspergillosis (40). Of the studies that have suggested that voriconazole prophylaxis prevents invasive aspergillosis and death (10), most have assessed voriconazole prophylaxis administered only in the immediate posttransplant period (i.e. 1–6 months after lung transplantation) and primary outcomes only until 12 months after transplant (41). Nonetheless, many patients receive much longer durations of voriconazole exposure related to additional targeted prophylaxis in the setting of increased immunosuppression for allograft rejection or for treatment of fungal colonization or an invasive infection. It may be that the benefits of
voriconazole prophylaxis in the immediate posttransplant period do not extend long term. A multicenter randomized clinical trial is still needed to determine the true efficacy of voriconazole prophylaxis in lung transplant recipients (39).

Our study has particular strengths. It is the first study to assess risk for voriconazole-associated SCC in lung transplant recipients weighed against the benefits of reducing invasive aspergillosis and death. As a 21-year, single-center, retrospective cohort study, there was access to detailed medical records for all cohort members including specific dates and durations of drug exposure in temporal relation to development of SCC, Aspergillus colonization, invasive aspergillosis and death. Primary outcomes were screened and identified by ICD-9 code but also confirmed by defined pathologic or clinical criteria. We used statistically rigorous methods and adjusted our models for a number of known risk factors for our primary outcomes. In addition, our expanded cohort of 455 lung transplant recipients significantly increased our study power compared with our previous work and validated our prior findings (16).

This study also had limitations. First, a number of confounding risk factors were not controlled for in our regression models; however, we believe that we included and controlled for major confounders. Due to incomplete data, we were unable assess smoking history, which is a known risk factor for SCC (20). In addition, we were unable to retrospectively obtain the Fitzpatrick skin type or relative sun exposure of cohort members. Despite this limitation, we believe it is unlikely that these variables differed by voriconazole exposure. Second, we captured only outpatient voriconazole administration and did not assess inpatient exposure. Consequently, we may have overestimated the relative impact of each unit of voriconazole exposure in our cumulative-dose models. Third, the EORTC criteria that we used to define cases of invasive aspergillosis may overestimate cases of invasive fungal infections in the lung transplant recipient patient population. This is because there is a more heterogeneous range of radiologic findings in lung transplant patients with or without true invasive fungal infections after transplant; however, we used a standard definition that has been used in other lung transplant studies (42,43). We do not believe misclassification of this outcome applies to a large proportion of our cases, and if such misclassification did occur, it would likely be nondifferential by voriconazole exposure status and would only bias our results toward the null.

Finally, we were unable to control for relative type and intensity of immunosuppression. At UCSF, maintenance immunosuppression has typically been accomplished with a combination of antiproliferative agents, calcineurin inhibitors and systemic steroids. In the late 1990s, our routine choice for calcineurin inhibitors switched from cyclosporine to tacrolimus. In 2004, our choice of antiproliferative agent switched from azathioprine to mycophenolatemofetil. Our use of corticosteroid dosing has not changed substantially over the past two decades. Analytically, we included year of transplant (era effect) in our multivariate analysis, and that may have accounted for differences in immunosuppression that varied over the 21-year study period. In fact, inclusion of this variable had a significant impact on selected analyses, particularly those assessing the relationship between voriconazole exposure and all-cause mortality. Although there is no universally accepted measure of relative level of immunosuppression, future studies could incorporate assessments of indicators including episodes of rejection, type, dose, and duration of immunosuppression and other heterogeneous health and immune-related phenotypes to better control for this variable.

In summary, we found that voriconazole exposure was independently associated with risk for SCC in lung transplant recipients, that this relationship was dose dependent and that it was specific to voriconazole among the antifungals examined. Patients with older age at transplant, white race and male sex were the most at risk. We also found that voriconazole exposure significantly reduced the risk of developing Aspergillus colonization, especially during the first year after transplant. Voriconazole exposure significantly reduced all-cause mortality, but this benefit was limited to those who developed posttransplant Aspergillus colonization.

These findings have important implications for the care of lung transplant recipients. SCCs in solid organ transplant recipients behave aggressively and can result in significantly reduced quality of life, metastatic disease, and increased mortality (2,44). It is important for physicians to be aware of the impact of voriconazole on these outcomes. As such, we recommend that all providers counsel lung transplant recipients on skin cancer education and photoprotection in addition to scheduling routine skin cancer screening with a trained dermatologist after transplantation (8). Lung transplant programs should also consider patient-specific risk factors when deciding on the type, dose and duration of antifungal prophylaxis regimens. In particular, the risks and benefits of voriconazole prophylaxis should be weighed carefully. Among lung transplant recipients with risk factors for SCC including those with older age, male sex and white race or those in whom prolonged voriconazole administration may not have clear benefit, such as patients lacking evidence of Aspergillus colonization, transplant physicians should consider limiting exposure to high doses of voriconazole or using alternative pharmacologic options that do not pose an increased risk for SCC.

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Voriconazole in Lung Transplant Recipients

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Demographic characteristics, cases versus controls by primary outcomes.

Table S2: Any exposure expanded multivariate Cox regression models by primary outcomes.

Table S3: Expanded hazard ratio for invasive aspergillosis and all-cause mortality by voriconazole exposure and stratified by Aspergillus colonization status.