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Comparing Azole Plasma Trough Levels in Lung Transplant Recipients: Percentage of Therapeutic Levels and Intrapatient Variability

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Background: This study compared therapeutic azole plasma trough levels (APL) of the azole antimycotics itraconazole (ITR), voriconazole (VOR), and posaconazole (POS) in lung transplant recipients and analyzed the influencing factors. In addition, intrapatient variability for each azole was determined.

Methods: From July 2012 to July 2015, 806 APL of ITR, VOR, posaconazole liquid (POS-Liq), and posaconazole tablets (POS-Tab) were measured in 173 patients of the Munich Lung Transplantation Program. Therapeutic APL were defined as follows: ITR, ≥700 ng/mL; VOR, 1000–5500 ng/mL; and POS, ≥700 ng/mL (prophylaxis) and ≥1000 ng/mL (therapy).

Results: VOR and POS-Tab reached the highest number of therapeutic APL, whereas POS-Liq showed the lowest percentage (therapy: ITR 50%, VOR 70%, POS-Liq 38%, and POS-Tab 82%; prophylaxis: ITR 62%, VOR 85%, POS-Liq 49%, and POS-Tab 76%). Risk factors for subtherapeutic APL of all azoles were the azole dose (ITR, $P < 0.001$; VOR, $P = 0.002$; POS-Liq, $P = 0.006$) and age over 60 years (ITR, $P = 0.003$; VOR, $P = 0.002$; POS-Liq, $P = 0.039$; POS-Tab, $P < 0.001$). Cystic fibrosis was a significant risk factor for subtherapeutic APL for VOR and POS-Tab (VOR, $P = 0.002$; POS-Tab, $P = 0.005$). Double lung transplantation (LTx) was significantly associated with less therapeutic APL for VOR and POS-Liq (VOR, $P = 0.030$; POS-Liq, $P < 0.001$). Concomitant therapy with 80 mg pantoprazole led to significantly fewer therapeutic POS APL as compared to 40 mg (POS-Liq, $P = 0.015$; POS-Tab, $P < 0.001$). VOR displayed the greatest intrapatient variability (46%), whereas POS-Tab showed the lowest (32%).

Conclusions: Our study showed that VOR and POS-Tab achieve the highest percentage of therapeutic APL in patients with LTx; POS-Tab showed the lowest intrapatient variability. APL are significantly influenced by azole dose, age, cystic fibrosis, type of LTx, and comedication with proton-pump inhibitors. Considering the high number of subtherapeutic APL, therapeutic drug monitoring should be integrated in the post-LTx management.

Key Words: itraconazole, voriconazole, posaconazole, therapeutic drug monitoring, lung transplantation

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INTRODUCTION

Itraconazole (ITR), voriconazole (VOR), and posaconazole (POS) are extended spectrum azole antimycotic agents. Because of their broad-spectrum activity, they play a crucial role in therapy and prophylaxis of fungal infections. Lung transplant recipients represent a patient population particularly at risk for the development of fungal infections. The reason for this is the permanent immunosuppressive therapy and other predisposing factors, such as the constant exposure of the allograft to the environment.[1–3] Fungal infections occur in 15%–35% of all lung transplantations (LTx) with mortality rates of up to 60%.[4] Several studies have shown a decreased incidence of fungal infections with antifungal prophylaxis.[5–7] A worldwide survey analyzing the current antifungal prophylactic strategies showed that most transplant centers already use prophylactic antimycotic drugs, with azoles being the preferred agents.[8]

Despite their effectiveness in antifungal prophylaxis and therapy, azoles are known to display a marked interpatient and intrapatient variability, caused by variable absorption, complex pharmacokinetics, and a distinct potential for drug interactions.[8–12] Therapeutic drug monitoring (TDM)

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can optimize the efficacy and safety of an antimycotic regimen with azoles.[13,14] To date, most studies concerning TDM of azole antimycotics in antifungal therapy or prophylaxis have been conducted primarily in patients with hematologic malignancies. However, the applicability in lung transplant recipients is not fully known.[13,15] Furthermore, to the best of our knowledge, no other studies have evaluated ITR, VOR, and POS for the therapy and prophylaxis of *Aspergillus* infections in a homogenous group of patients.

In 2012, the Lung Transplantation Program of the Ludwig-Maximilians-Universität (LMU) Munich established a new comprehensive approach in the follow-up management of lung transplant recipients including a series of surveillance measures. One part of this innovation consisted of the analysis of antifungal therapy at follow-up visits. A routine TDM of azole plasma trough levels (APL) of ITR, VOR, and POS administered for treatment and prophylaxis of fungal infections in lung transplant recipients was performed.

Therefore, the primary aim of this retrospective study was to use these data to investigate the differences in the percentage of therapeutic APL for ITR, VOR, and POS in lung transplant recipients in the real-life setting. In addition, we wanted to identify relevant factors influencing the percentage of therapeutic APL and to assess the differences in intrapatient variability to establish the most reliable choice of antifungal therapy and prophylaxis in lung transplant recipients.

MATERIALS AND METHODS

Study Design and Standard Care of Lung Transplant Recipients

From July 2012 to July 2015, we retrospectively analyzed all APL of ITR, VOR, and POS measured in adult lung transplant recipients of the Munich Lung Transplantation Program of the LMU Munich. This analysis was approved by the local board of medical ethics at LMU Munich (approval number: 144-14). Demographic and clinical data including daily dose and dosage form of the administered azole antimycotic were obtained from medical records and computerized databases. Patients received no induction therapy and were maintained with standard care triple immunosuppression with corticosteroids, tacrolimus, and mycophenolate mofetil, as described previously.[16]

Inclusion and Exclusion Criteria

All blood samples of adult lung transplant recipients, who were in routine follow-up within the Munich Lung Transplant Program and treated with ITR capsules, VOR tablets, and posaconazole liquid (POS-Liq) or posaconazole tablets (POS-Tab), were included. Blood tests for the determination of APL, tacrolimus plasma trough levels, and cytomegalovirus load are part of the standard procedure at every follow-up visit of lung transplant recipients.

Blood samples were excluded, if the azole was used to boost the tacrolimus plasma level, as only subtherapeutic azole doses were used for this purpose. Further exclusion criteria were omitted azole doses before measurement, unknown azole or proton-pump inhibitor (PPI) doses, APL measurement before reaching steady state, and the use of an intravenous azole formulation. Steady state was assumed after 5 days of therapy with POS and VOR and after 7 days of therapy with ITR.[17–19]

Azole Doses and Dosage Forms

ITR capsules were administered at a dose of 200 mg twice daily for therapy and prophylaxis.[1,20] VOR tablets were started with a loading dose of 400 mg twice daily on day 1, followed by a maintenance dose of 200 mg twice daily for therapy and prophylaxis.[1,20,21] POS-Liq was administered at a dose of 400 mg twice daily for therapy and 200 mg thrice daily for prophylaxis.[22] The therapy and prophylaxis with POS-Tab was initiated with a loading dose of 300 mg twice daily on day 1 and continued once daily at a dose of 300 mg.[23] As the results and the effectiveness of the new approach in the follow-up management of lung transplant recipients were analyzed retrospectively, there were no dose adjustments because of the achieved APL.

Patients were advised to take ITR capsules, POS-Liq, and POS-Tab with a fatty meal or at least with a carbonated beverage to improve absorption.[22,24–26] Patients being treated with VOR were told to take VOR tablets 1 hour before or after food intake.[21,27]

Serum Samples and Drug Assay

Blood sampling for azoles was performed along with immunosuppressants during follow-up visits. The serum samples for azoles and immunosuppressants were drawn immediately before the administration of the azole and immunosuppressant, and therefore represent trough levels. Patients were instructed to take their medication after these blood tests. The measurement of trough levels was chosen because of the reliability and practicability of the parameter to draw interpatient and intrapatient comparisons.

Quantification of the azole compounds in the serum was performed by liquid chromatography–tandem mass spectrometry using a commercially available, fully validated, and IVD-CE-labeled kit (MassTox TDM Series A—Antimykotika, Order Numbers 92,111 and 92,922; Chromsystems Instruments & Chemicals, GmbH, Graefelfing, Germany). This method is based on a stable isotope dilution. The lower limit of detection for ITR, VOR, and POS was 20 ng/mL.

Definitions and End Points

Lung transplant recipients received azoles as either therapy or prophylaxis. Since July 2012, azole prophylaxis has been uniformly administered to all patients after LTx, usually for the duration of 6 months posttransplant. If *Aspergillus* species were isolated or a positive *Aspergillus* galactomannan antigen was detected in transbronchial biopsy, bronchoalveolar lavage, endotracheal suction, or blood, a lifelong azole therapy was administered. As there was no internal guideline on the choice of antimycotic agent, the selection was based on a case-by-case decision by the treating physician.

Applied target APL in this study were defined according to the TDM guidelines for antifungal agents by the British Society for Medical Mycology.[13] For ITR, the target APL were defined as $\geq$700 ng/mL to ensure an adequate drug level in

treatment and prophylaxis.[13,14,28] Because there is evidence that VOR APL above 5500 ng/mL are associated with a higher incidence of adverse events, such as hepatotoxicity, neurotoxicity, and visual disturbances, we adopted a target APL of 1000–5500 ng/mL for treatment and prophylaxis.[13,29–31] For POS, different target thresholds were applied for treatment and prophylaxis. A prophylactic threshold was set at ≥700 ng/mL and a therapeutic threshold at ≥1000 ng/mL, respectively.[13,31,32] APL reaching the applied target threshold for therapy or prophylaxis were considered therapeutic. For VOR, APL were considered therapeutic between 1000 and 5500 ng/mL.

The range of median APL defined the interpatient variability, whereas intrapatient variability was described using the coefficient of variation of the same patient with an unchanged azole and PPI dose. Therefore, a high coefficient of variation represents a high intrapatient variability.[33] Older age was defined as 60 years or older.[34]

The primary end point consisted of the percentage of therapeutic APL for ITR, VOR, and POS in lung transplant recipients in the real-life setting. Additional end points were factors influencing the percentage of therapeutic APL and differences in intrapatient variability to be able to assess the most reliable choice of antifungal agent for patients with LTx.

Statistical Methods

Statistical analyses were conducted using IBM SPSS Statistics 23 and Microsoft Excel 2013. Demographic data and outcomes between groups were compared using χ^2 test for categorical variables and Mann–Whitney U test and Kruskal–Wallis test for continuous variables. Results were expressed using 2-tailed P values and considered statistically significant at $P < 0.05$. To avoid overrepresentation of patients with numerous APL measured, one median or mean level per patient was used for the analysis of mean and median APL.

A multivariate binary logistic regression with forward selection with an alpha level of 5% was applied to detect the effect of potential explanatory variables [ie, azole daily dose, age, body mass index (BMI), underlying disease, type of transplantation, and comedication] on therapeutic APL. For the binary logistic regression analysis, all APL were included to analyze the effect of the observed covariates on every APL measured.

RESULTS

In total, 981 APL of 193 lung transplant recipients were measured consecutively with 175 APL being excluded. The various reasons for exclusion are shown in Figure 1. The most frequent causes were omitted azole doses before measurement and the use of an azole to boost the tacrolimus plasma level.

The remaining 806 APL originated from 173 patients. During the study period, 46 patients received more than one azole or different POS dosage forms at different points in time and were included in the analysis for each azole separately. Of about 41% (n = 332) of all APL measured were applied for prophylaxis, and 59% (n = 474) for therapy. Patient demographics are shown in Table 1.

APL and Therapeutic Plasma Trough Levels

The highest median APL were achieved with POS-Tab (2123 ng/mL), whereas the lowest were observed for POS-Liq (592 ng/mL) (Table 2). Of about 62% of all APL measured for prophylaxis and 65% of all APL measured for therapy were considered therapeutic. The maximum target threshold was exceeded by 10 (5%) VOR APL.

When comparing achieved APL in prophylactic versus therapeutic use, no significant differences between the median achieved APL were found (ITR: P = 0.264; VOR: P = 0.708; POS-Liq: P = 0.700; POS-Tab: P = 0.732). To

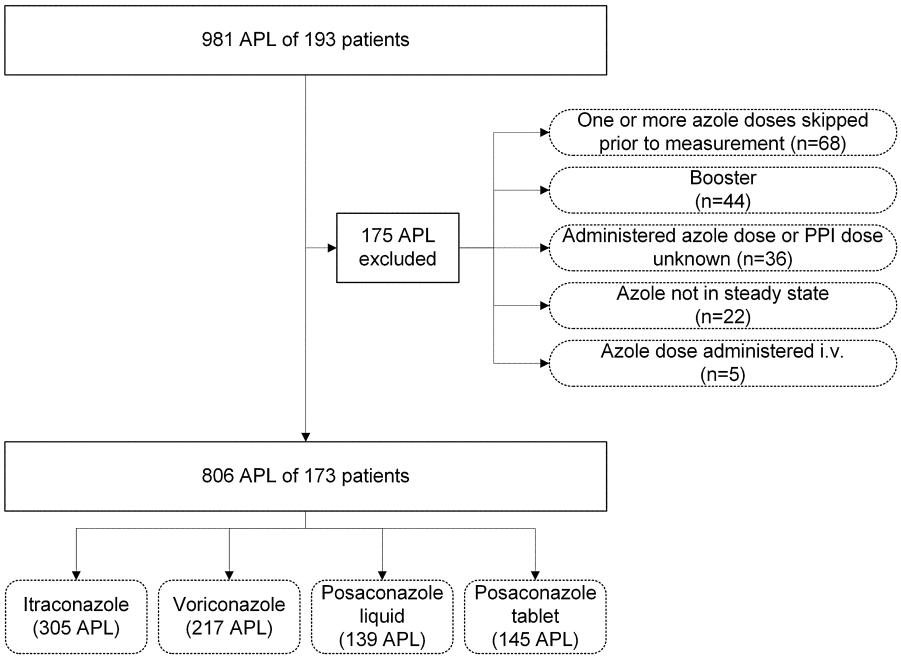

FIGURE 1. Exclusion criteria. Excluded APL listed according to the different reasons for exclusion.

TABLE 1. Patient Demographics and Transplant Characteristics

Variable	Total	ITR	VOR	POS-Liq	POS-Tab
No. of patients	173	89	64	43	32
No. of APL	806	305 (38%)	217 (27%)	139 (17%)	145 (18%)
No. of APL per patient (mean ± SD)	4.7 ± 5.5	3.4 ± 3.2	3.4 ± 3.5	3.2 ± 4.2	4.5 ± 8.1
Azole use					
Prophylaxis	332 (41%)	265 (87%)	13 (6%)	37 (27%)	17 (12%)
Therapy	474 (59%)	40 (13%)	204 (94%)	102 (73%)	128 (88%)
Age (mean ± SD)	51.4 ± 13.4	51.5 ± 13.2	51.1 ± 13.2	55.0 ± 11.9	54.0 ± 13.1
Gender					
Male	95 (55%)	57 (64%)	34 (53%)	24 (56%)	17 (53%)
Female	78 (45%)	32 (36%)	30 (47%)	19 (44%)	15 (47%)
BMI (mean ± SD)	21.3 ± 3.7	21.6 ± 3.7	20.8 ± 3.6	21.3 ± 3.9	20.4 ± 3.4
Type of LTx					
Single LTx	54 (31%)	30 (34%)	19 (30%)	14 (33%)	14 (44%)
Double LTx	119 (69%)	59 (66%)	45 (70%)	29 (67%)	18 (56%)
Underlying disease					
CF	31 (18%)	16 (18%)	14 (22%)	3 (7%)	3 (9%)
COPD	47 (27%)	27 (30%)	19 (30%)	13 (30%)	11 (34%)
Lung fibrosis	70 (40%)	38 (43%)	22 (34%)	20 (47%)	12 (38%)
PH	6 (3%)	1 (1%)	1 (2%)	3 (7%)	3 (9%)
Misc	19 (11%)	7 (8%)	8 (13%)	4 (9%)	3 (9%)
Time elapsed since LTx (median, yrs ± range)	1.0 (0–12)	0.0 (0–12)	2.0 (0–11)	1.0 (0–11)	1.0 (0–9)
PPI therapy					
Pantoprazole	690 (86%)	269 (88%)	157 (72%)	126 (91%)	138 (95%)
Omeprazole	15 (2%)	6 (2%)	5 (2%)	3 (2%)	1 (<1%)
Esomeprazole	26 (3%)	6 (2%)	6 (3%)	9 (6%)	5 (3%)
No PPI	75 (9%)	24 (8%)	49 (23%)	1 (<1%)	1 (<1%)

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; misc, miscellaneous; PH, pulmonary hypertension.

evaluate the effect of the covariates' daily dose, underlying disease, age, BMI, type of LTx, and comedication with PPI on therapeutic APL, a binary logistic regression analysis was conducted.

Azole Daily Dose

An obvious factor that influences APL is the azole daily dose. Recommended azole daily doses were administered in 80% (n = 644) of all APL measured. Table 3 shows median APL according to the applied azole daily doses. The azole daily dose had a significant effect on the number of therapeutic APL of all analyzed azoles apart from POS-Tab (ITR: $P < 0.001$; VOR: $P = 0.002$; POS-Liq: $P = 0.006$). Figure 2 depicts the distribution of APL with the most frequently administered daily dose for each azole. Median APL and the percentage of therapeutic APL in relation to different covariates and measured under recommended azole daily doses are depicted in Table 4.

TABLE 2. Mean and Median APL

Indication	Azole	Daily Dose, mg	No. of Patients	Mean ± SD, ng/mL	Median, ng/mL	Min, ng/mL	Max, ng/mL	Therapeutic APL, %
Prophylaxis	ITR	400	79	1155 ± 852	1055	20	4203	62
	VOR	400	4	1826 ± 846	2107	600	2800	85
	POS-Liq	600	13	808 ± 596	592	50	1933	49
	POS-Tab	300	7	2709 ± 2906	2123	50	8698	76
Therapy	ITR	400	10	779 ± 506	801	30	1669	50
	VOR	400	60	2173 ± 2061	1628	20	11,878	70
	POS-Liq	800	31	930 ± 682	765	30	2424	38
	POS-Tab	300	25	2509 ± 1495	2107	405	4843	82

Max, maximum APL; Min, minimum APL.

TABLE 3. Azole Plasma Levels Classified by Administered Daily Doses

Azole	No. of Patients	No. of APL	Daily Dose, mg	Mean ± SD, ng/mL	Median, ng/mL	Min, ng/mL	Max, ng/mL	Therapeutic APL, %
ITR	4	9	100	55 ± 34	47	20	120	0
	19	64	200	667 ± 575	489	30	2767	38
	2	19	300	532 ± 486	351	110	2075	26
	71	203	400	1368 ± 960	1189	97	5885	74
	2	10	800	949 ± 487	887	398	1671	60
VOR	1	2	100	593 ± 486	593	249	937	0
	12	25	200	969 ± 864	705	20	2900	40
	1	2	300	213 ± 124	213	125	300	0
	58	181	400	2177 ± 1828	1900	20	11,878	77
	1	1	500	1000 ± 0	1000	—	—	100
	1	2	600	3650 ± 3606	3650	1100	6200	100
	1	4	800	1174 ± 1134	846	196	2806	25
POS-Liq	2	3	300	1045 ± 407	1202	583	1350	67
	6	20	400	455 ± 348	420	49	1411	5
	11	25	600	974 ± 678	942	50	2468	68
	28	91	800	1008 ± 636	899	30	2944	41
POS-Tab	32	144	300	2778 ± 1607	3115	50	8698	81
	1	1	400	1179 ± 0	1179	—	—	100

Marked in gray: recommended azole daily doses for therapy and prophylaxis.

Underlying Disease

APL of patients with cystic fibrosis were significantly lower than APL of all other underlying diseases ($P < 0.001$). In particular, only 33 (49%) of the 68 APL of patients with cystic fibrosis, measured under recommended azole daily doses, were therapeutic ($P < 0.001$). Cystic fibrosis remained a significant risk factor for subtherapeutic APL for VOR tablets and POS-Tab using regression analysis (VOR: $P = 0.002$; POS-Tab: $P = 0.005$).

Age

The mean age of patients in our study was 51 ± 13 years. Using regression analysis, therapeutic APL of patients older and younger than 60 years were compared. For all azoles, age >60 years was associated with fewer subtherapeutic APL (ITR: $P = 0.003$; VOR: $P = 0.002$; POS-Liq: $P = 0.039$; POS-Tab: $P < 0.001$). Therefore, younger patients (<60 years) were at a higher risk for subtherapeutic APL.

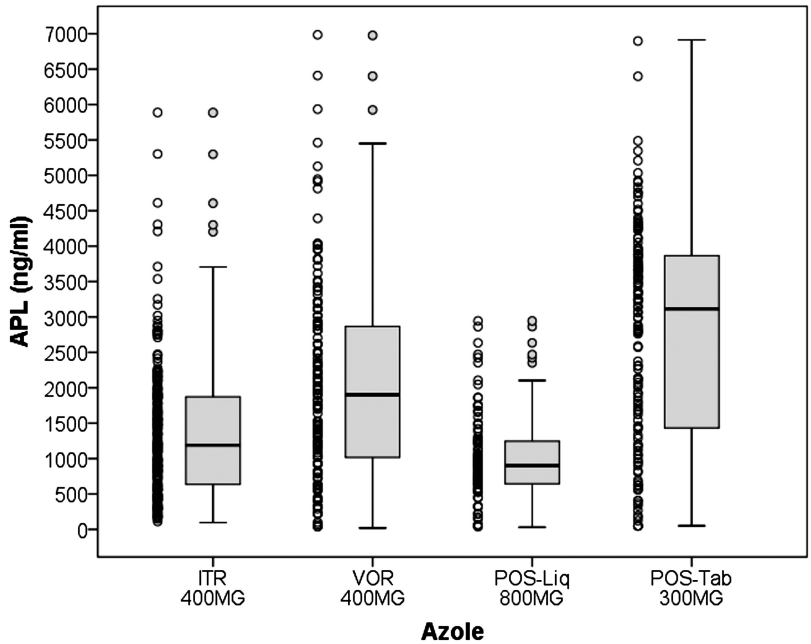

FIGURE 2. Median APL. Achieved APL of the most frequent azole daily doses combining a scatter plot and a box-and-whisker plot. Target APL for therapy and prophylaxis were defined as follows: ITR, ≥700 ng/mL; VOR, 1000–5500 ng/mL; and POS: ≥700 ng/mL (prophylaxis); and ≥1000 ng/mL (therapy).

TABLE 4. Univariate Analysis of APL Under Therapeutic Azole Doses in Relation to the Different Covariates

	ITR (400 mg/d)				VOR (400 mg/d)			
Covariate	**No. of Patients**	**No. of APL**	**Median APL, ng/mL**	**Therapeutic APL, %**	**No. of Patients**	**No. of APL**	**Median APL, ng/mL**	**Therapeutic APL, %**
Age, yrs								
Under 60	47	136	1104	71	38	105	1800	68
Over 60	26	67	1411	81	21	76	2105	89
BMI								
≤25	62	160	1201	76	55	165	1900	75
>25	14	43	987	65	8	16	2003	94
Type of LTx								
Single LTx	25	67	1330	79	19	77	2198	81
Double LTx	46	136	1121	71	39	104	1800	74
ULD								
CF	8	13	932	69	13	40	954	50
Non-CF	63	190	1224	74	45	141	2068	84
PPZ, mg								
40	62	149	1158	74	37	88	1504	75
80	17	38	1126	68	16	34	2000	68
	POS-Liq (800 mg/d)				**POS-Tab (300 mg)**			
Covariate	**No. of Patients**	**No. of APL**	**Median APL, ng/mL**	**Therapeutic APL, %**	**No. of Patients**	**No. of APL**	**Median APL, ng/mL**	**Therapeutic APL, %**
Age, yrs								
Under 60	13	28	724	39	20	56	1649	59
Over 60	15	63	899	40	12	88	3563	96
BMI								
≤25	25	73	811	36	30	127	3003	80
>25	4	18	1095	56	4	17	3717	88
Type of LTx								
Single LTx	13	49	734	18	14	90	3349	90
Double LTx	15	42	1226	64	18	54	2219	67
ULD								
CF	1	1	2424	100	3	13	620	23
Non-CF	27	90	883	39	29	131	3256	87
PPZ, mg								
40	21	68	915	43	21	108	3368	87
80	6	14	603	21	10	25	1058	56

Non-CF, all underlying diseases apart from CF; PPZ, pantoprazole; ULD, underlying disease.

Body Mass Index

The mean BMI was 21 ± 3.7. Using logistic regression, we compared a BMI >25 with a BMI ≤25. A BMI >25 was significantly associated with a lower percentage of therapeutic APL for ITR (ITR: $P = 0.031$). This effect was not detectable for VOR and POS.

Type of Transplantation

Of the 173 patients included in our study, about onethird patients underwent single LTx ($n = 54$; 31%). Regression analysis demonstrated that for VOR and POS-Liq, single lung transplant recipients had significantly more therapeutic APL (VOR: $P = 0.030$; POS-Liq: $P < 0.001$). For the remaining azoles, the type of LTx was not a significant risk factor for subtherapeutic APL.

Proton-pump Inhibitors

Of about 91% ($n = 731$) of all APL analyzed in our study were measured with concomitant PPI therapy. Because 86% ($n = 690$) of all patients received pantoprazole as a PPI, only the concomitant therapy with different pantoprazole doses (40 and 80 mg) was analyzed. A higher dose of pantoprazole was significantly associated with lower APL. This effect could be observed for both dosage forms (POS-Liq prophylaxis: $P = 0.038$; POS-Liq therapy: $P = 0.011$; POS-Tab: $P < 0.001$). Furthermore, the effect of 80-mg pantoprazole on POS APL is confirmed by a significantly lower number of therapeutic APL. With 40-mg pantoprazole, 52% ($n = 46$) of all POS-Liq APL and 87% ($n = 94$) of all POS-Tab APL were therapeutic. Administering 80-mg pantoprazole concomitantly resulted in 19% ($n = 3$) and 56% ($n = 14$) of therapeutic POS APL for

POS-Liq and POS-Tab, respectively (POS-Liq: $P = 0.015$; POS-Tab: $P < 0.001$). APL in relation to the different pantoprazole doses are shown in Table 4. The PPI dose did not yield significant results using regression analysis.

Intrapatient Variability

The large range of mean and median APL reflects the large interpatient variability. To depict the intrapatient variability, we analyzed patients with more than one APL measured, receiving an identical azole and pantoprazole dose. The results show a high intrapatient variability for all azoles characterized by the coefficient of variation. VOR showed the greatest variability with a coefficient of variation of 46%. The lowest intrapatient variability was seen for POS-Tab (32%). ITR and POS-Liq reached 40% and 37%, respectively.

DISCUSSION

This study monitored APL of all azoles available during the study period for therapy and prophylaxis of *Aspergillus* infections in lung transplant recipients. Other studies dealing with the TDM of azoles mainly address the use of one specific azole and were mostly conducted in patients with hematological malignancies.[13,15] Furthermore, our study comprised a large number of APL measured in a real-life setting and collected over a period of 3 years.

Our study demonstrates that APL of lung transplant recipients are subject to a high interpatient and intrapatient variability. Our findings confirm the importance of TDM to identify patients at risk for subtherapeutic APL, which is in line with the findings of Mitsani et al and Andes et al.[14,35] In addition, risk factors for low APL and subtherapeutic APL have been identified. A lower age is associated with a lower number of therapeutic APL for all azoles analyzed. Cystic fibrosis as an underlying disease was related to the lowest APL of all lung transplant recipients and thus represents a significant risk factor for subtherapeutic APL for VOR and POS-Tab. Comedication with PPI can be considered a third risk factor, particularly affecting POS APL. Patients treated with 80-mg pantoprazole achieved significantly fewer therapeutic APL for both POS formulations. Furthermore, double LTx was associated with less therapeutic APL.

The administration of recommended daily doses of ITR, VOR, and POS-Liq was necessary to achieve therapeutic APL. Lower doses resulted in median APL below the minimal target thresholds. Furthermore, the administered daily dose was significantly associated with the number of therapeutic APL for all azoles analyzed. Because of the retrospective design of the study, reasons for doses deviating from the recommendation could not be established.

The applied azole target thresholds were derived from the 2014 guideline of the British Society for Medical Mycology, which was the most recent guideline at the time of data collection. These guidelines are mostly in line with the guideline published in 2016 by the International Society for Heart and Lung Transplantation, which applies a higher target threshold for POS therapy (1200 ng/mL) and a lower target threshold for ITR used for prophylaxis (500 ng/mL).[36]

Median prophylactic levels did not differ significantly from median therapeutic levels. Therefore, the indication had no relevant effect on achieved APL and is not discussed separately. The highest APL were noted for POS-Tab and VOR. POS-Tab's APL were similar to the results of Miceli et al and Durani et al,[37,38] who analyzed APL in a predominantly hemato-oncological patient population. Median VOR APL were higher than those in previous studies dealing with patients with transplant and patients with hematological malignancies.[9,39] The lowest APL were noted for POS-Liq with the results being similar to those found by Lebeaux et al and others in patients with hematological malignancies.[40–42] The median APL for POS-Tab were tripled compared with POS-Liq, whereas other studies showed mostly a 2-fold increase in APL.[37,38,43–45] Previous studies have found higher ITR APL in patients with acquired immunodeficiency syndrome[46] and lower levels in patients who are neutropenic[47] compared with our results in lung transplant recipients. This indicates that the results in patients with other underlying diseases cannot be extrapolated to lung transplant recipients in general.

Our data confirmed the great interpatient variability found by other researchers.[17,18,48] Hence, the number of therapeutic APL for each individual azole is of interest. The results varied depending on the azole and analyzed covariates. Younger age was a risk factor for all azoles. Patients aged less than 60 years achieved significantly lower APL than patients who were older. For VOR and POS, these results have been previously described by Mitsani et al and Shields et al.[35,49] Kohl et al explained the influence of age with a lower volume of distribution in patients who were older and therefore support our findings.[50] By contrast, Okuda et al and Sansone-Parsons et al did not confirm age to be the risk factor for low ITR and POS APL. However, the studies either included only a small number of patients or analyzed healthy volunteers.[51,52]

The type of LTx (double LTx) was a risk factor for subtherapeutic VOR and POS-Liq levels. We could not explain this finding, and no other studies investigating the type of transplantation as a risk factor for low APL were identified. Despite the substantial number of APL included in the regression analysis for both types of LTx, this finding needs to be confirmed in a larger patient cohort.

Our study also demonstrated that cystic fibrosis as an underlying disease was associated with low APL and a higher percentage of subtherapeutic APL for all azoles. Significantly, less therapeutic APL were found for VOR and POS-Tab in patients with cystic fibrosis. However, the overall validity of the results for POS-Tab is limited because of its small sample size in cystic fibrosis lung transplant recipients. Nevertheless, repeated measurements for each patient confirm the low number of therapeutic APL. There are few studies dealing solely with cystic fibrosis lung transplant recipients. Billaud et al recommended dose escalation in patients with cystic fibrosis LTx of 35%–45% compared with standard recommended dose, which is in line with our results.[53]

Comedication with PPI represented a significant risk factor for low POS APL. The influence of drugs altering

gastric acidity on POS APL has been well described.[24,54,55] Patients receiving a higher dose of pantoprazole had a significantly lower ratio of therapeutic POS APL. This effect was seen for both POS formulations. In contrast to our findings, Kraft et al reported that POS-Tab's APL were not significantly altered by drugs influencing the gastric pH.[56] However, the analyzed PPI was esomeprazole at a dose of 40 mg daily in healthy subjects. Even if POS APL measured in patients taking 80-mg pantoprazole were still above the therapeutic target, special caution should be exercised with patients already at risk for low POS APL. Although other studies have observed lower ITR APL with a comedication with PPI,[57] our data showed no statistically relevant effect.

Although our study has pointed out relevant risk factors for subtherapeutic APL in lung transplant recipients, we recognized inherent limitations. The number of APL measured differs considerably between the various azoles and underlying diseases because we analyzed routinely measured APL. As there was no consistent documentation of adverse events and toxicity, these outcomes could not be analyzed. The clinical impact of the azole therapy or prophylaxis was also not evaluated, as the primary focus of this retrospective study was on achieved APL and influencing factors. Nevertheless, several studies have already shown a correlation between APL and patient outcome,[14,15,35,58,59] which underlines the significance of TDM, to identify patients at risk for subtherapeutic APL.

CONCLUSION

In conclusion, our study showed that achieved therapeutic APL in lung transplant recipients vary considerably between the different azoles analyzed. Most patients treated with VOR or POS-Tab reached therapeutic APL. However, up to 30% of these APL were below the minimal required target thresholds for therapy and prophylaxis. Furthermore, our results demonstrated that the underlying disease cystic fibrosis, comedication with PPI, the azole daily dose, the type of LTx, and the age of the patient significantly influence APL of lung transplant recipients. Especially for patients with one or more risk factors for low APL, we recommend TDM as part of standard care to ensure therapeutic APL. POS-Liq and POS-Tab's APL should, in particular, be monitored closely when comedication with higher doses of PPI is started or stopped.

Considering the percentage of therapeutic APL and the intrapatient variability, POS-Tab seem to be the most reliable choice of antimycotic therapy in lung transplant recipients.

Further prospective studies are needed to analyze the effect of low APL and risk factors for low APL on the clinical outcome in lung transplant recipients and the most feasible intervals for TDM.

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