

Comparison of the safety and cost-effectiveness of nebulized liposomal amphotericin B and amphotericin B deoxycholate for antifungal prophylaxis after lung transplantation

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25 ***Authorship Statement***

26 All authors meet ICMJE authorship criteria. KU, YK, and MN conceptualized and
27 designed the study. KU drafted the manuscript, and YK, SN, DH, and TT critically
28 reviewed it. MN provided critical advice as an expert in clinical microbiology. YY, ST,
29 AO, DN, HD, and MN supervised the treatment. All the authors contributed to and
30 approved the final version of the manuscript.

31

Abstract¹

Introduction: Fungal infection after lung transplantation can lead to poor clinical outcome, for which lung transplant recipients require prophylaxis. One of the antifungal agents used after lung transplantation is nebulized amphotericin B (AMB). Nebulized AMB causes adverse events such as dyspnea and airway irritation, and long-term use leads to high economic costs. So far, prophylactic regimens employing AMB deoxycholate (AMB-d) and liposomal AMB (L-AMB) have been developed. This study compared the efficacy, safety, and cost of AMB-d and L-AMB.

Patients and Methods: Patients who underwent lung transplantation at Kyoto University Hospital from January 2021 to May 2023 were included in this study. Thirty-three patients received nebulized AMB-d, whereas 29 received nebulized L-AMB.

Results: Both regimens maintained comparable prophylactic efficacy regarding the development of fungal infection in the AMB-d and L-AMB groups (3.0% vs. 3.4%, $P=0.877$). Patients treated with nebulized L-AMB experienced fewer respiratory-related adverse reactions than those treated with nebulized AMB-d (6.9% vs. 30.3%, $P<0.05$), leading to a longer treatment duration with L-AMB than with AMB-d. Additionally, the

¹**Abbreviations:** AMB, amphotericin B; AMB-d, amphotericin B deoxycholate; L-AMB liposomal amphotericin B

48 daily cost of administering L-AMB was lower than that of administering AMB-d (3,609
49 Japanese Yen vs. 1,792.3 Japanese Yen, $P<0.05$).

50 *Discussion:* These results suggest that nebulized L-AMB is safer and more cost-effective
51 than nebulized AMB-d, with comparable efficacy.

52

53 ***Keywords***

54 Nebulized liposomal amphotericin B, nebulized amphotericin B deoxycholate, lung
55 transplantation, fungal prophylaxis, pharmacoeconomics

56

Introduction

Lung transplant recipients have a high risk of acquiring infectious diseases, including fungal infections [1–3]. Therefore, they require prophylaxis with antifungal agents such as voriconazole, itraconazole, and nebulized amphotericin B (AMB) [4]. The efficacy of inhaled AMB for prophylaxis after lung transplantation has been demonstrated [2,5,6]. Inhaled AMB formulations include AMB deoxycholate (AMB-d), AMB lipid complex, and liposomal AMB (L-AMB). Various dosing regimens utilizing these formulations have been reported [2,7,8]. However, several challenges are associated with AMB nebulization. Insoluble precipitates in AMB formulations can occlude the ventilator circuit, leading to dyspnea or reduced tidal volume. Additionally, AMB can irritate the airways, leading to coughing and bronchospasm. These adverse events may limit the continuation of AMB therapy. Moreover, long-term administration of AMB inhalation is costly.

At Kyoto University Hospital (our institution), nebulized AMB-d and oral itraconazole have been administered for fungal infection prophylaxis after lung transplantation. In June 2022, Fungizone® (AMB-d) became temporarily unavailable in Japan owing to shipment restrictions. This triggered a change in regimen from AMB-d to L-AMB at our institution. Nebulized L-AMB, owing to its retained activity as a liposomal

formulation [9], allows a reduced inhalation frequency [2,10,11]. Thus, the risk of adverse events and the cost associated with administering nebulized AMB were expected to decrease with this change in regimen. This study aimed to compare the safety, efficacy, and cost of AMB administration to patients who underwent lung transplantation before and after the change in AMB regimen.

Patients and Methods

Study design

This retrospective study included patients who underwent lung transplantation at Kyoto University Hospital from January 2021 to May 2023. Electronic medical records were reviewed, and pertinent data were retrieved. Patient characteristics, antifungal prophylactic properties, as well as inhalation efficacy, safety, and cost, were compared between the AMB-d and L-AMB groups. This study was approved by the Ethics Committee of the Graduate School of Medicine of Kyoto University (R0545-2).

Prophylactic regimen

A total of 62 patients received nebulized AMB and oral itraconazole, except two patients in the AMB-d group who died before itraconazole administration and three

patients in the L-AMB group who received voriconazole because of pre-existing lung aspergillosis. Thirty-three patients who underwent lung transplantation from January 2021 to May 2022 received nebulized AMB-d, whereas 29 who underwent lung transplantation from June 2022 to May 2023 received nebulized L-AMB. Completion of prophylactic inhalation was defined as treatment continuation until the patient was discharged.

The dosing regimens of AMB inhalation were determined based on the previous reports [2,8], with slight modification to facilitate implementation at our institution. For AMB-d inhalation, 5 mg of Fungizone® suspended in 10 mL of sterile water was inhaled per dose by both adults and children. AMB-d inhalation was administered thrice daily from postoperative day 1 until discharge. For L-AMB inhalation, 25 mg of AmBisome® suspended in 6 mL of sterile water was inhaled per dose for adults and 10 mg for children weighing <20 kg. L-AMB inhalation was performed once daily on Mondays, Wednesdays, and Fridays (three doses/week) within 2 weeks after transplantation. Afterward, it was administered once weekly on Mondays (one dose/week) until discharge.

Evaluation of efficacy

Efficacy was evaluated based on the absence of fungal infections up to 6 months

after transplantation including periods of hospitalization and post-discharge. Fungal infections were regularly monitored using chest radiography, computed tomography, sputum culture, and serum β -(1,3)-D glucan and *Aspergillus* galactomannan antigens.

Evaluation of safety

Safety evaluations included checks for filter occlusion in the ventilator circuit and respiratory-related symptoms during and immediately after inhalation. Filter occlusion was defined as an apparent reduction in tidal volume. Respiratory-related symptoms were defined as symptoms unrelated to filter occlusion but associated with AMB, such as dyspnea and bronchospasm.

Evaluation of daily cost of AMB

The daily cost of AMB administration was calculated by dividing the total cost of AMB administered by the duration of the inhalation prophylaxis. The total cost of AMB was calculated using the drug price in Japan (¥1,203/vial for Fungizone[®] and ¥7,647/vial for AmBisome[®]).

Statistical analysis

Continuous variables were analyzed using the Mann–Whitney U test, and categorical variables were analyzed using Fisher’s exact test. Kaplan–Meier curves were analyzed using log-rank test. P -values were considered statistically significant at $P<0.05$. All analyses were performed using GraphPad Prism version 9.2.0 (GraphPad Software, Boston, MA).

Results

Patient characteristics

Table 1 shows the patient characteristics. No significant differences were observed between the groups except in the percentage of deceased/living donors.

Comparison of efficacy and safety

The efficacy and safety of AMB-d were compared to those of L-AMB (Table 2). One case of bronchial aspergillosis occurred 3 months after transplantation in AMB-d group, whereas one case in L-AMB group developed pulmonary scedosporiosis 4 months after transplantation. Table 3 shows the characteristics of these patients. The patient in AMB-d group underwent left single-lung transplantation from a deceased donor for interstitial lung disease after hematopoietic stem cell transplantation. At 29 days post-

transplant, AMB-d was discontinued because the physicians determined that the risk of fungal infection had decreased. Additionally, the serum concentration of itraconazole plus hydroxyitraconazole was 1485.5 ng/mL, which was sufficient. [12] Subsequently, the patient was cured with oral voriconazole and a systemic L-AMB injection. The patient in the L-AMB group underwent double-lung transplantation from a deceased donor for peripheral pulmonary artery stenosis. L-AMB inhalation was continued until discharge. Neither AMB nor itraconazole had poor sensitivity against the infected *Scedosporium*. This patient was cured with a systemic voriconazole injection.

Next, the number of cases with safety problems were compared (Table 2). The L-AMB group had significantly fewer safety problems than the AMB-d group ($P=0.018$). The incidence of respiratory-related symptoms, especially dyspnea, was significantly lower in the L-AMB group (6.9%) than in the AMB-d group (30.3%). The percentage of patients who continued inhalation is shown in Figure 1. In the AMB-d group, inhalation led to discontinuation immediately after transplantation, resulting in only 42.4% of patients completing the treatment. In contrast, 82.8% of the patients in the L-AMB group completed the treatment. Figure 2 shows the detailed reasons for AMB-inhalation discontinuation. Cases in which AMB-inhalation was discontinued due to safety problems such as filter occlusion were found only in AMB-d group.

Comparison of cost

Table 2 lists the costs of AMB treatment. The daily cost of treatment in the L-AMB group was significantly lower than that in the AMB-d group despite a lack of difference in total cost.

Discussion

Owing to its formulation characteristics, L-AMB can reduce the frequency of inhalation compared to AMB-d [2,10,11]. This study revealed that the regimen change from AMB-d to L-AMB significantly improved safety. Although dyspnea was observed, no other respiratory-related symptoms, such as pharyngeal discomfort or bronchospasm, were observed in the L-AMB group. This could be due to the reduction in the dosing frequency and liposomalization of AMB. A previous study showed that the nebulized AMB lipid complex, which is not available in Japan, was superior to nebulized AMB-d in safety profile [13]. Based on the results of this group and ours, addition of lipids to or liposomalization of AMB might have mitigated the airway irritation associated with AMB. However, the mechanism underlying this phenomenon is unknown, and is one of the issues to be investigated in the future to improve nebulized antibiotic therapy.

183 Among the patients who were administered AMB-d, one developed bronchial
184 aspergillosis after discontinuing AMB therapy. As aspergillosis following lung
185 transplantation can lead to life-threatening complications [1,4], the duration of AMB
186 inhalation after lung transplantation should be further investigated. In the present study,
187 *Scedosporium* infection in the L-AMB group could not be prevented with this
188 prophylactic regimen because of its poor sensitivity to AMB and itraconazole.

189 Previous studies have evaluated the cost of antifungal prophylaxis after
190 hematopoietic stem cell transplantation [14,15]. However, no study on lung
191 transplantation has been reported. The price of L-AMB per dose was higher than that of
192 AMB-d, but the decrease in dose frequency reduced the daily cost. This study revealed
193 that L-AMB administration did not reduce the total drug costs compared to AMB-d
194 administration. This was due to improvements in safety and prophylactic duration in the
195 L-AMB group. Inappropriate discontinuation of prophylaxis can lead to the development
196 of fungal infections, further increasing overall treatment costs. Therefore, the current
197 results suggest that L-AMB is superior to AMB-d in terms of cost-effectiveness. However,
198 future studies are required to address the optimal duration for fungal infection prophylaxis
199 with AMB and its related cost-effectiveness.

201 AMB for fungal infection prophylaxis is not subject to reimbursement by the
202 public insurance system, including in Japan. AMB inhalation is recommended,
203 considering its clinical benefits [2,5,6]. The current findings suggest that L-AMB
204 inhalation offers superior safety and cost-effectiveness compared to AMB-d inhalation,
205 with comparable efficacy. Thus, it is a viable option for prophylaxis against fungal
206 infections after lung transplantation.

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214

215 **Ethical Approval**

216 This observational study was prepared in compliance with the “Guidelines for the
217 protection of patient privacy in medical papers, including case reports and presentations
218 at academic conferences.” This study was approved by the Ethics Committee of the
219 Graduate School of Medicine of Kyoto University (R0545-2).

220

221 **Declaration of Interest**

222 None.

223

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277 **Tables**

278 Table 1. Comparison of patient characteristics and antifungal prophylaxis between the AMB-d and L-AMB groups

	Total (n=62)	AMB-d (n=33)	L-AMB (n=29)	<i>P</i>-value
Patient characteristics				
Sex (female/male)	32/30	14/19	18/11	0.137
Age	44 [2–64]	44 [3–63]	44 [2–64]	0.777
Height (cm)	162.1 [83.0–184.5]	163.9 [83.0–181.7]	161.1 [84.0–184.5]	0.394
Weight (kg)	47.8 [8.3–85.4]	48.2 [12.0–81.9]	49.5 [8.3–85.4]	0.287
Indication for transplantation				
Idiopathic interstitial pneumonia	13 (21.0%)	7 (21.2%)	6 (20.7%)	1.000
Interstitial lung disease after HSCT	11 (17.7%)	8 (24.2%)	3 (10.3%)	0.194
Pulmonary hypertension	10 (16.1%)	3 (9.1%)	7 (24.1%)	0.167
Others	28 (45.2%)	15 (45.5%)	13 (44.8%)	1.000
Type of transplantation				
Deceased donor/living donor	48/14	22/11	26/3	<u>0.037</u>
Double/single	45/17	22/11	23/6	0.393
Length of hospitalization after transplantation (days)	65 [17–258]	67 [17–227]	63 [35–258]	0.278
Acute rejection	29 (46.8%)	17 (51.5%)	12 (41.4%)	0.456
Antifungal prophylaxis properties				
Number of cases who completed inhaled prophylaxis	38 (61.3%)	14 (42.4%)	24 (82.8%)	<u>0.002</u>

Serum concentration of ITCZ plus hydroxy-ITCZ (ng/mL) *	1147.3 [527.8–2777]	1068.4 [527.8–2777]	1224.3 [767.7–2562.2]	0.208
Serum concentration of voriconazole (µg/mL) *	N/A	N/A	2.67 [1.49–3.52]	N/A
Inhaled prophylaxis duration (days)	48 [5–193]	42 [5–148]	53 [32–193]	<u>0.036</u>
Total number of doses	N/A	124 [15–444]	12 [8–33]	<u><0.0001</u>
Cumulative amounts of doses (mg)	N/A	620 [75–2220]	300 [90–825]	N/A

279 *P*-values <0.05 were considered statistically significant, as shown in bold and underlined letters. The median [minimum– and maximum]
280 values are shown.

281 AMB, amphotericin B; HSCT, hematopoietic stem cell transplantation; ITCZ, itraconazole

282 * Two patients in the AMB-d group did not receive ITCZ because of mortality before initiating ITCZ treatment. In the L-AMB group,
283 three patients had pre-existing lung aspergillosis and were administered voriconazole instead of ITCZ.

284 Table 2. Comparison of the efficacy, safety, and cost between the AMB-d group and L-AMB groups

	Total (n=62)	AMB-d (n=33)	L-AMB (n=29)	P-value
Efficacy				
Fungal infection after lung transplantation	2 (3.2%)	1 (3.0%)	1 (3.4%)	0.877
Safety				
Cases with safety problems *	23 (37.1%)	17 (51.5%)	6 (20.7%)	<u>0.018</u>
Filter occlusion	15 (24.2%)	11 (33.3%)	4 (13.8%)	0.085
Respiratory-related symptoms (Details of respiratory-related symptoms)	12 (19.4%)	10 (30.3%)	2 (6.9%)	<u>0.026</u>
Dyspnea	12 (19.4%)	10 (30.3%)	2 (6.9%)	<u>0.026</u>
Decreased SpO ₂	2 (3.2%)	2 (6.1%)	0 (0%)	0.494
Pharyngeal discomfort	2 (3.2%)	2 (6.1%)	0 (0%)	0.494
Bronchospasm	2 (3.2%)	2 (6.1%)	0 (0%)	0.494
Cyanosis	1 (1.6%)	1 (3.0%)	0 (0%)	1.000
Cough	1 (1.6%)	1 (3.0%)	0 (0%)	1.000
Cost				
Daily cost of AMB (Japanese Yen/day)	N/A	3,609 [2,062.3–3609]	1,792.3 [1,282.1–2,294.1]	<u>≤0.0001</u>
Total cost of AMB (Japanese Yen)	N/A	126,852 [15,345–454,212]	91,764 [61,176–252,351]	0.214

285 *P*-values <0.05 were considered statistically significant, as shown in bold and underlined letters. The median [minimum– and maximum]
286 values are shown.
287 SpO₂, oxygen saturation
288 * Some patients experienced multiple safety problems.

289 Table 3. Characteristics of patients who developed fungal infection

Patient number	1	2
AMB formulation	AMB-d	L-AMB
Sex	Female	Male
Age (years)	44	44
Height (cm)	157.8	174.2
Weight (kg)	43.3	85.4
Indication for transplantation	Interstitial lung disease after HSCT	Peripheral pulmonary artery stenosis
Type of transplantation	Left single-lung from a deceased donor	Double-lung from a deceased donor
Length of hospitalization after transplantation (days)	58	54
Acute rejection	—	—
Inhaled prophylaxis	Discontinued at 29 days post-transplant	Completed
Serum concentration of ITCZ plus hydroxy-ITCZ (ng/mL)	1485.5	1628
Inhaled prophylaxis duration (days)	29	47
Total number of doses	85	11
Cumulative amounts of doses (mg)	425	275
Fungal infection after lung transplantation	Bronchial aspergillosis	Pulmonary scedosporiosis
Adverse events with AMB inhalation	None	None
Daily cost of AMB (Japanese Yen/day)	3,526	1,789.7
Total cost of AMB (Japanese Yen)	86,955	84,117

291 **Figure legend**

292 Figure 1. Percentage of patients in each group continuing nebulized AMB therapy

293 *P*-values, hazard ratios, and 95% confidence intervals (CIs) are shown at the top right

294 corner of the graph. Numbers of patients at risk of fungal infection at 0, 25, 50, 75, 100,

295 125, 150, and 175 days after transplantation are also shown at the bottom of the graph.

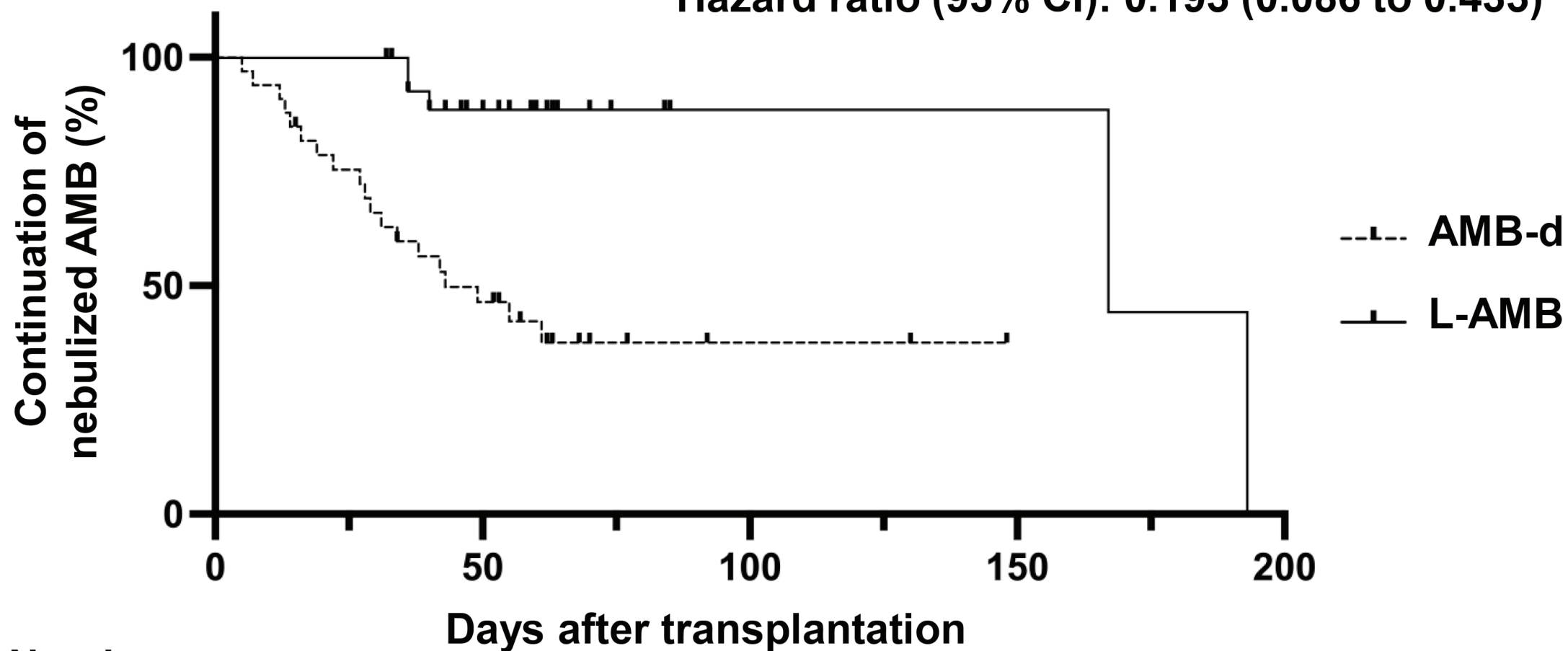
296

297 Figure 2. Detailed reasons for AMB-inhalation discontinuation

298 Safety problems are shown in color, whereas other reasons are shown with black shading.

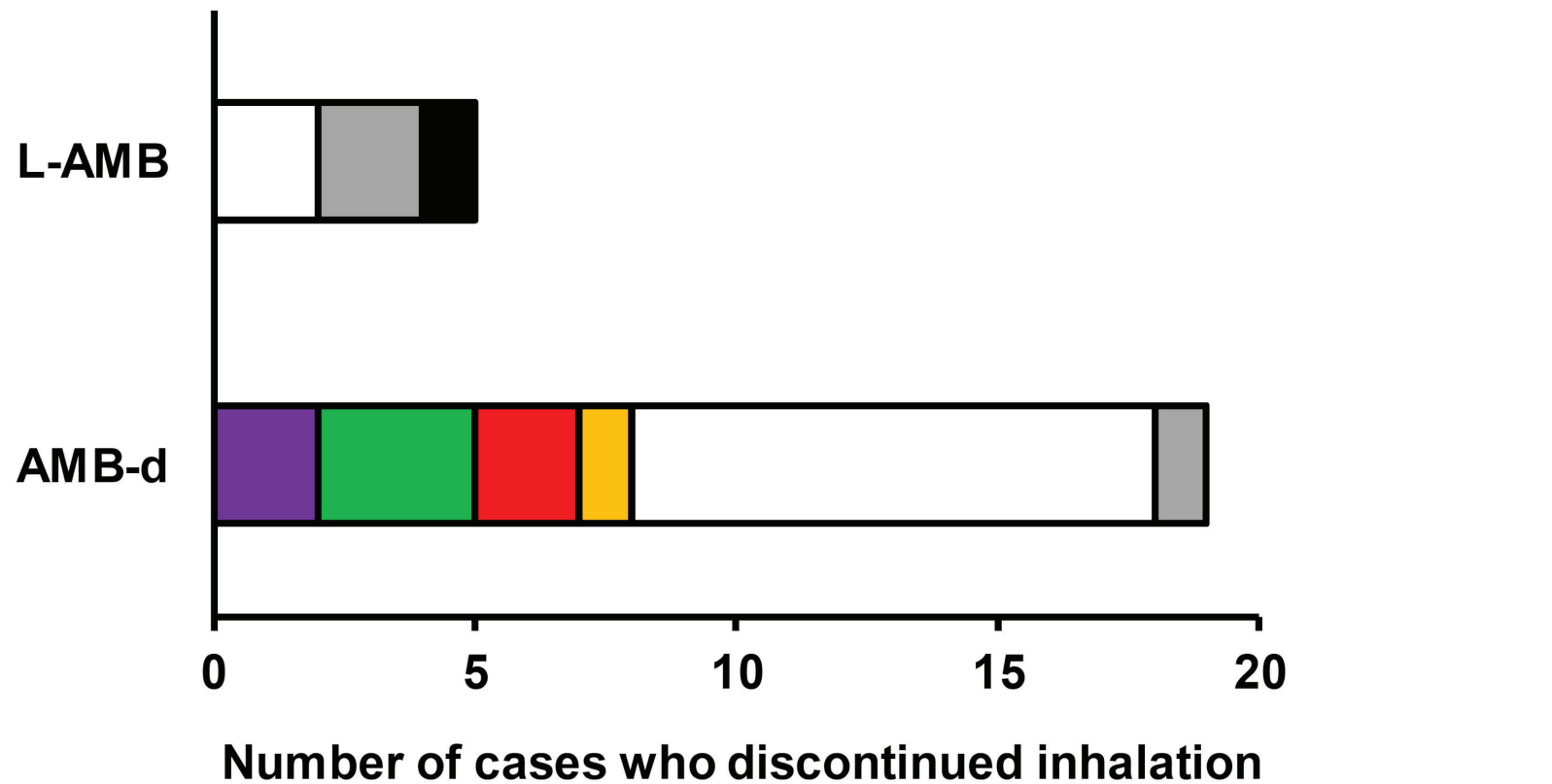
$P = 0.0001$

Hazard ratio (95% CI): 0.193 (0.086 to 0.433)



**Number
at risk**

AMB-d	33	25	15	5	3	3	1	1
L-AMB	29	29	16	5	3	3	3	2



 Filter occlusion

 Dyspnea

 Bronchospasm

 Pharyngeal discomfort

 Decreased infection risk

 Long-term hospitalization

 Transition to best supportive care