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Primary Therapy for Invasive Aspergillosis With Triazoles or L-AmB: A Multicenter Retrospective Study

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Objective. To compare clinical outcomes of patients treated with liposomal amphotericin B (L-AmB) versus mold-active triazoles as primary treatment for invasive aspergillosis (IA).

Methods. Retrospective study of adult patients treated with either L-AmB or triazoles for proven or probable IA at 2 academic hospitals over a 10-year period. The primary endpoint was all-cause 90-day mortality from IA diagnosis. Landmark trial emulation at day 7 postdiagnosis was used to compare initial triazole versus L-AmB for IA. Confounding by indication was addressed using inverse probability of treatment weighting (IPTW) with stabilized weights, and treatment effects were estimated using Cox regression with both IPTW and covariate adjustment.

Results. Overall, 401 patients were included. Median age 65 (interquartile range 56–74) years, 60.8% male. Main predisposing conditions were: hematologic malignancy 151 (37.7%), severe respiratory viral infection 120 (29.9%), and chronic steroid treatment 64 (16%). Overall, 105 (26.2%) patients received L-AmB and 296 (73.8%) triazoles as initial therapy. Patients on L-AmB were more likely to have therapy changed (63.8% vs 17.2%, $P < .001$) for switching to oral triazoles (48, 71.6%), while the main reason for changing triazoles was adverse events (23, 45.1%). Overall 90-day survival rates were similar between triazole (58.8%; 95% confidence interval [CI], 53.4–64.7) and L-AmB (53.3%, 44.6–63.8) groups ($P = .3$). IPTW-weighted Kaplan-Meier survival curves from day 7 landmark demonstrated an adjusted hazard ratio of 1.43 (95% CI, 0.87–2.33; $P = .61$).

Conclusions. Primary L-AmB therapy was well tolerated and associated with similar survival rates as triazoles. Further studies are needed to investigate the impact of primary L-AmB on IA patient outcomes.

Keywords. invasive aspergillosis; L-AmB; triazoles.

Despite changes in epidemiology and risk factors, invasive aspergillosis (IA) still has high morbidity and mortality rates. Over the past decade, described risk factors for IA have broadened beyond classical disease states such as hematologic malignancies (HM) and solid organ transplantation (SOT) to include patients with chronic pulmonary diseases, chronic steroid treatment, and prolonged ICU hospitalization [1, 2]. Similarly, high rates of IA have been reported in patients with acute respiratory distress syndrome secondary to viral infections, such as influenza or, more recently, SARS-CoV-2 [3, 4]. Mortality rates could range from 10%–35% in solid organ transplantation [5] to 55%–60% in COVID-19-associated pulmonary aspergillosis and refractory acute leukemia [6, 7]. Prompt infection diagnosis and antifungal treatment administration are the cornerstones for IA management. Historically, guidelines recommend voriconazole as first-line treatment [8], and recently 2 different randomized trials demonstrated similar rates of success with isavuconazole [9] and posaconazole [10]. Liposomal amphotericin B (L-AmB) is suggested as alternative choice [8]. Indeed, as there are limited comparative data between L-AmB and mold-active triazoles as primary treatment for IA, even though L-AmB is frequently used in patients with refractory or breakthrough IA. Nevertheless, the efficacy of triazole therapy can be compromised by pharmacokinetic variability, drug-drug interactions, hepatic and central nervous toxicities, and increasing rates of azole-resistant IA, which requires clinicians to use L-AmB as initial therapy in selected patients [11–13]. Given this background, we retrospectively analyzed the epidemiology and outcome of patients with probable or proven IA, according to predisposing risk factors and initial antifungal treatment.

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MATERIALS AND METHODS

Study Design, Population, and Setting

This is a multicenter retrospective observational study of all consecutive adult (≥18 years) patients diagnosed of probable or proven IA during hospitalization, over a 10-year period (January 2013–December 2022), at 2 tertiary teaching hospitals from northern Italy: IRCCS S. Orsola Hospital (center A), and Humanitas Research Hospital, Milan (center B). Patients who died without receiving any dose of antifungal were excluded. The study was approved by the Ethic Committee of the promoting center (n° 624/2022/Oss/AOUBo). Informed consent was obtained contacting patients via email or phone call. In case of deceased or unreachable patients, the informed consent was waived considering the observational nature of the study.

Study Procedures and Definitions

Patients were identified through pharmacy records, microbiological data and clinical charts. Proven or probable IA was defined according to updated European Organization for Research and Treatment of Cancer-Mycoses Study Group Education and Research Consortium consensus [14], and the recent FUNDICU consensus on probable invasive pulmonary aspergillosis and tracheobronchial aspergillosis in nonneutropenic adult critically ill patients definitions [15].

Endpoint Variables

The primary endpoint was all-cause 90-day mortality from IA diagnosis (defined as the date of positive diagnostic sample). We also examined all-cause 42-day mortality from IA diagnosis to facilitate comparisons with recent randomized clinical trials. Secondary endpoints included radiological and mycological findings, which were recorded at IA diagnosis and during follow-up, specifically at 30- and 90-day within IA diagnosis.

Exposure Variable

For descriptive analysis, we considered the first antifungal started after IA diagnosis. For causal comparisons (landmark cohort) we further restricted to patients who (1) were alive at day 7 and (2) had initiated either triazole or L-AmB within those first 7 days. Antifungal doses, routes of administration, and serum therapeutic drug concentrations were recorded when available. Data about any change on antifungal treatment were collected. Adverse events emerging during initial antifungal treatment were recorded according to the Common Toxicity Criteria classification.

Covariates

We analyzed other patient variables, including demographic data (age and sex), comorbidities according to Charlson comorbidity index (CCI) [16], specific underlying conditions favoring IA development including hematological malignancy (HM), solid organ transplantation (SOT), chronic steroid use defined as a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days [14], chronic pulmonary diseases [1], viral-associated pulmonary aspergillosis (VAPA) according with proposed criteria [17, 18], ICU stay during more than 14 days at the IA diagnosis was also recorded as well as undergoing recent (<30 days) major surgery. Previous antifungal exposure was considered within 90 days from IA diagnosis. The ICU stay at the time of IA diagnosis was also recorded.

Mycological Data

Characteristics of mycological diagnosis included the type of sample collected (blood, serum, bronchoalveolar lavage, tissue) and the test performed (direct examination, culture, galactomannan (GM) index, *Aspergillus* spp. polymerase chain reaction) with results.

Statistical Analysis

Categorical variables were reported as counts and percentage. Continuous variables were expressed as mean ± SD if normally distributed, or as median and interquartile range (IQR) if non-normally distributed. For the univariate analysis, categorical variables were compared using χ^2 test or Fisher exact test as appropriate, whereas continuous variables were compared using Student *t*-test or Mann–Whitney *U* test depending on whether data were normally distributed.

To address immortal time bias, we employed a landmark analysis at day 7 postdiagnosis [19]. Patients were included if they survived beyond day 7, initiated therapy within this period, and received either triazole or L-AmB. Follow-up extended from the landmark to day 90 or death (Supplementary Figures 1 and 2).

We used inverse probability of treatment weighting (IPTW) to address confounding by indication [20]. Propensity scores were estimated via logistic regression using triazoles as the reference treatment with the final model including clinically relevant baseline covariates: hematological malignancy, chronic steroid use, liver disease, and antifungal prophylaxis. Propensity score distributions were inspected for evidence of positivity violations. Extreme weights were rare but present, reflecting limited overlap in some baseline covariates between treatment groups. We therefore reported effective sample sizes, standardized mean differences before and after weighting, and weight distribution summaries (see Supplementary Figure 3, 4 and 5). Unadjusted and final IPTW-weighted model were therefore developed (Supplementary Figure 6, 7, and 8). As a sensitivity analysis, we repeated all models after truncating weights at the 1st and 99th percentiles, which yielded results consistent with the primary analysis (Supplementary Figures 9 and 10). Stabilized weights were calculated, with covariate balance assessed using standardized mean differences (<0.1 indicating adequate balance) [21].

The final treatment model employed Cox proportional hazards regression with both IPTW and covariate adjustment. Covariates for the final model were selected on the basis of univariate analysis ($P < .1$) and clinical plausibility. We evaluated proportional hazards assumptions using Schoenfeld residuals from Cox models and graphical diagnostics (scaled Schoenfeld plots), which did not suggest systematic departures from proportionality (Supplementary Figure 11).

Model performance was evaluated through Harrell C-index for discrimination and calibration plots at several timepoints. Additional diagnostics including residual analysis, influence statistics (DFBETA), and multicollinearity assessment (variance inflation factors) (Supplementary Figure 12, 13 and 14). The E-value was used in sensitivity analysis to assesses the robustness or initial treatment selection versus mortality in relation to potential unmeasured or uncontrolled confounding [22]. Poisson regression with person-time (antifungal exposure days) as an offset was used to estimate the incidence rate ratios for adverse effects with confidence intervals in antifungal treatment groups.

Statistical analyses were performed using R version 4.5.0 with packages for survival analysis, propensity score weighting, and balance assessment (detailed in Supplementary methods). Significance was set at $\alpha = 0.05$ (2-sided).

RESULTS

Overall, 401 patients with a diagnosis of IA (proven 16, 4.0%; probable 385, 96.0%) were enrolled during the study period, 288 (71.8%) in center A and 113 (28.2%) in center B (Table 1). Median age was 65 (IQR 56–74) years, of which 60.8% were male, with a median CCI of 5 (IQR 3–6). The main predisposing condition was hematological malignancy in 151 (37.7%) patients, followed by VAPA (120, 29.9%), chronic steroid treatment (64, 16%), and chronic pulmonary diseases (64, 16%). Overall, 105 (26.2%) patients received initial treatment with L-AmB and 296 (73.8%) with triazoles, mostly voriconazole (272, 91.9%), with 24 (8.1%) receiving primary isavuconazole and none posaconazole. Overall, 18 (4.5%) received combination therapy with higher rates among L-AmB compared with triazole groups (9.5% vs 2.7%, $P = .004$). Among 296 patients initiating triazole therapy, 46 (15.5%) modified their treatment regimen at a median of 13 days (IQR: 7–23 days) after diagnosis, with 122 (41.2%) experiencing 90-day mortality. Of 105 patients initiating L-AmB, 66 (62.9%) switched to alternative therapy at a median of 10 days (IQR: 7–15 days), with 49 (46.7%) dying within 90 days. Combination treatment consisted of echinocandins in all cases, no adverse events related to echinocandin administration were reported.

Time to Treatment

The median time from IA diagnosis to first dose administration was 0 (IQR 0–3) and 0 (IQR 0–1) ($P = .004$) for triazoles versus L-AmB, respectively, with more patients in triazole group skewing toward delay in time to treatment initiation after diagnosis (Supplementary Figures 1 and 2). The comparison of baseline variable between patients initially treated with triazoles or L-AmB showed significant differences for the following variables: age (median 66 [IQR 58–75] versus 61 [IQR 49–70] years), CCI (median 5 [3–6] versus 4 [3–6]), HM (30.4% vs 58.1%), neutropenia (10.5% vs 21.0%), chronic steroid treatment (18.9% vs 7.6%), previous prolonged ICU stay (11.5% vs 2.9%), VAPA (34.1% vs 18.1%), antifungal prophylaxis at diagnosis (17.9% vs 58.1%) (Table 1).

All-cause 42-day and 90-day mortality rates were similar between patients receiving primary triazole or L-AmB therapy. For triazoles day +42 and +90 survival rates were 70.3% (95% confidence interval [CI], 65.3–75.7) and 58.8% (95% CI, 53.4–64.7), respectively, versus for L-AmB 65.7% (95% CI, 57.2–75) and 53.3% (95% CI, 44.6–63.8). At day 90, 167 (66.3%) and 91 (35.1%) patients had clinical resolution of symptoms and radiological complete resolution of findings, respectively, without differences between groups (Supplementary Table 1).

Adverse Effects

The timeline of antifungal therapy, including the timing of changes within 90-day from IA diagnosis is shown in Figure 1. Most L-AmB-treated patients (67/105, 63.8%) had their antifungal therapy changed during treatment. The most common reasons included: switch to oral therapy (48, 71.6%), refractory IA (8, 11.9%), adverse events (7, 10.4%), and persistent IA (2, 3%). Therapeutic changes in patients on primary triazoles were reported in 51/296 (17.2%) patients, with reasons including adverse effects (23, 45.1%), persistent IA (13.7%), and refractory IA (13.7%) (Table 1). As for L-AmB, in all 7 patients reporting adverse events, stage 1 and stage 2 acute kidney injury according to RIFLE criteria were observed in 5 and 2 cases, respectively. As for triazoles, in 18/23 (78%) cases a clinically significant increase in liver enzymes were observed. When adjusted for antifungal exposure days, the overall incidence rates of adverse events did not differ between L-AmB and triazoles (incidence rate ratio 1.60; 95% CI, .66–4.42; $P = .27$).

Rates of microbiological positive testing were also assessed. Fungal cultures from nonsterile sites (mainly bronchoalveolar lavages) tested positive in 50.0% of cases (140/280), GM on bronchoalveolar lavage was positive in 92.2% of cases (333/361), serum GM was positive in 42.0% (87/207), and *Aspergillus* polymerase chain reaction in 70.5% (43/61) of tested patients (details of microbiological findings are summarized in Supplementary Table 2). Logistic regression analysis revealed that for each 1-point increase in the serum GM index, the odds of death at day 90 increased by 24.4% (odds ratio [OR]: 1.24; 95% CI, 0.97–1.60; $P = .09$).

Table 1. Characteristics of Study Population and Comparison Between First-line Antifungal Treatment

	Triazoles N = 296 (73.8%)	L-AmB N = 105 (26.2%)	Overall N = 401 (100%)
Enrolling center			
Center A	205 (69.3)	83 (79.0)	288 (71.8)
Center B	91 (30.7)	22 (21.0)	113 (28.2)
Demographic data			
Age (years) [median (IQR)]	66 (58–75)	61 (49–70)	65 (56–74)
Sex, male	176 (59.5)	68 (64.8)	244 (60.8)
Charlson comorbidity index (median, IQR)	5 (3–6)	4 (3–6)	5 (3–6)
Risk factors			
SOT	37 (12.5)	16 (15.2)	53 (13.2)
Liver	11 (29.7)	9 (56.3)	20 (37.7)
Kidney	3 (8.1)	0 (0)	3 (5.7)
Lung	11 (29.7)	4 (25.0)	15 (28.3)
Heart	10 (27.0)	3 (18.8)	13 (24.5)
Hematologic malignancy	90 (30.4)	61 (58.1)	151 (37.7)
HCT	27 (9.1)	26 (24.8)	53 (13.2)
AML	33 (11.1)	29 (27.6)	62 (15.5)
CLL	4 (1.4)	3 (2.9)	7 (1.7)
ALL	4 (1.4)	5 (4.8)	9 (2.2)
MM	10 (3.4)	4 (3.8)	14 (3.5)
Lymphoma	35 (11.8)	20 (19.0)	55 (13.7)
Neutropenia	31 (10.5)	22 (21.0)	53 (13.2)
Solid tumor	44 (14.9)	6 (5.7)	50 (12.5)
Chronic steroid treatment	56 (18.9)	8 (7.6)	64 (16.0)
COPD	53 (17.9)	11 (10.5)	64 (16.0)
ICU stay >14 d	34 (11.5)	3 (2.9)	37 (9.2)
Recent major surgery	17 (5.7)	5 (4.8)	22 (5.5)
Recent or concomitant severe respiratory viral infection (VAPA)	101 (34.1)	19 (18.1)	120 (29.9)
Antifungal prophylaxis at diagnosis	53 (17.9)	61 (58.1)	114 (28.4)
Ward of IA diagnosis			
Medical ward	208 (70.3)	83 (79.0)	291 (72.6)
ICU	88 (29.7)	22 (21.0)	110 (27.4)
Diagnosis classification			
Proven	13 (4.4)	3 (2.9)	16 (4.0)
Probable	283 (95.6)	102 (97.1)	385 (96.0)
Microbiological features			
Patients with invasive sampling	215 (72.6)	65 (62.5)	301 (75.1)
Any positive culture	106 (49.3)	34 (52.3)	148 (49.2)
Aspergillus isolation			
A. fumigatus	77 (26.0)	22 (21.0)	99 (24.7)
A. flavus	24 (8.1)	6 (5.7)	30 (7.5)
A. niger	8 (2.7)	3 (2.9)	11 (2.7)
A. terreus	9 (3.0)	1 (1.0)	10 (2.5)
A. nidulans	2 (0.7)	0 (0)	2 (0.5)
PCR performed	38 (12.8)	23 (21.9)	61 (15.2)
PCR positive	25 (65.8)	18 (78.3)	43 (70.5)
Median value (cp/mL, IQR)	3498 (662–8904)	3498 (803–8893)	3498 (668–7683)
GM on BAL performed	275 (92.9)	86 (81.9)	361 (90.0)
GM >1 on BAL	254 (92.4)	79 (91.9)	333 (92.2)
Median value (ODI, IQR)	3.5 (1.9–4.9)	3.7 (2.6–5.1)	3.6 (2.0–5.0)
Serum GM performed	123 (44.6)	75 (71.4)	207 (51.6)
GM >0.5 on serum	45 (34.1)	42 (56.0)	87 (42.0)
Median value (ODI, IQR)	1.5 (0.7–3.1)	1.2 (0.8–3.4)	1.3 (0.79–3.21)
Site of diagnosis			
Isolated pulmonary	274 (92.6)	91 (86.7)	365 (91.0)
Disseminated	19 (6.4)	10 (9.5)	29 (7.2)

Table 1. Continued

	Triazoles N = 296 (73.8%)	L-AmB N = 105 (26.2%)	Overall N = 401 (100%)
Radiological findings			
Nodules	144 (48.6)	57 (54.3)	201 (50.1)
Ground-glass opacity	182 (61.5)	55 (52.4)	237 (59.1)
Halo sign	30 (10.1)	17 (16.2)	47 (11.7)
Air crescent sign	6 (2.0)	0 (0)	6 (1.5)
Consolidation	177 (59.8)	54 (51.4)	231 (57.6)
Cavity	45 (15.2)	18 (17.1)	63 (15.7)
Pleural effusion	59 (19.9)	15 (14.3)	74 (18.5)
Initial antifungal treatment			
Voriconazole	272 (91.9)	0 (0)	272 (67.8)
L-AmB	0 (0)	105 (100)	105 (26.2)
Isavuconazole	24 (8.1)	0 (0)	24 (6.0)
Combination treatment	8 (2.7)	10 (9.5)	18 (4.5)
Time from IA diagnosis to antifungal initiation (days) (median)	0 (0–3)	0 (0–1)	0 (0–3)
Change to another antifungal	51 (17.2)	67 (63.8)	76 (73.8)
Voriconazole	3/51 (5.9)	39/67 (58.2)	42 (35.6)
Isavuconazole	21/51 (41.2)	26/67 (38.8)	47 (39.8)
Posaconazole	3/51 (5.9)	2/67 (3.0)	5 (4.2)
L-AmB	24/51 (47.1)	0/67 (0)	24 (20.3)
Reason to antifungal change			
Switch to oral therapy	3/51 (5.9)	48/67 (71.6)	51 (43.2)
Persisting IA	7/51 (13.7)	2/67 (3.0)	9 (7.6)
Refractory IA	7/51 (13.7)	8/67 (11.9)	15 (12.7)
Drug underexposure	3/51 (5.9)	0/67 (0)	2 (2.5)
Drug-drug interactions	3/51 (5.9)	0/67 (0)	3 (2.5)
Adverse event	23/51 (45.1)	7/67 (10.4)	30 (25.4)
Breakthrough candidemia	2/51 (3.9)	0 (0)	2 (1.7)
Days from antifungal start to change (median)	14 (8–30)	10 (7–16)	12 (7–21)
Overall antifungal treatment (days) (median, IQR)	44 (21–85)	47 (16–83)	45 (19–85)
All-cause death 30-day	86 (29.1)	35 (33.3)	121 (30.2)
All-cause death 90-day	122 (41.2)	49 (46.7)	171 (42.6%)
Days from IA diagnosis to death (median, IQR)	24 (11–45)	19 (10–41)	22 (10–44)

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; BAL, bronchoalveolar lavage; CLL, Chronic Lymphocytic Leukemia; COPD, chronic obstructive pulmonary disease; GM, galactomannan; HCT, Hematopoietic Cell Transplantation; IA, invasive aspergillosis; ICU, intensive care unit; IQR, interquartile range; L-AmB, liposomal amphotericin B; MM, Multiple Myeloma; ODI, Optical Density Index; PCR, polymerase chain reaction; SOT, solid organ transplantation; VAPA, viral-associated pulmonary aspergillosis.

Survival Analysis

In univariate analysis (Table 2), nonsurvivors were more likely to be older (68 [53–71] versus 63 [59–76] days, $P < .001$) and with higher median CCI (5 [3–7] versus 4 [3–6], $P < .001$). Other significant differences included higher frequencies of VAPA, ICU admission, and positive serum GM.

For triazoles, 272 (91.9%) of patients were treated by day 7, 16 deaths (5.41%) occurred before days 7. For L-AMB, 101 (96.2%) were treated before day 7, 9 deaths (8.57%) occurred before day 7 (Figure 2). Therefore landmark analysis at day 7 postdiagnosis was used in subsequent models to reduce potential immortal time bias. IPTW based on hematological malignancy, chronic steroid use, liver disease, and antifungal prophylaxis achieved good covariate balance, with all standardized mean differences reduced to <0.1 after weighting (Supplementary Figure 4). The distribution of stabilized weights was centered near 1, with few extreme values, and the effective sample size remained adequate in both treatment groups (Supplementary Table 2). Graphical inspection of Schoenfeld residuals did not indicate meaningful departures from proportional hazards. Sensitivity analyses with weight truncation at the 1st and 99th percentiles produced results consistent with the primary analysis. Inverse probability treatment weighting reduced standardized mean differences for all covariates, with model diagnostics supporting the robustness of the IPTW matching between the 2 treatment groups (Supplementary Figure 4).

The results of the final treatment model (IPTW and covariate-adjusted treatment model) are shown in Figures 3 and 4. Initial L-AmB versus triazoles was associated with an 83-day (landmark to day 90) adjusted hazard ratio of 1.43 (95% CI, 0.87–2.33; $P = .61$), indicating a nonsignificantly higher rate of mortality. Model fit, discrimination, and diagnostics were acceptable without evidence of violation of proportional

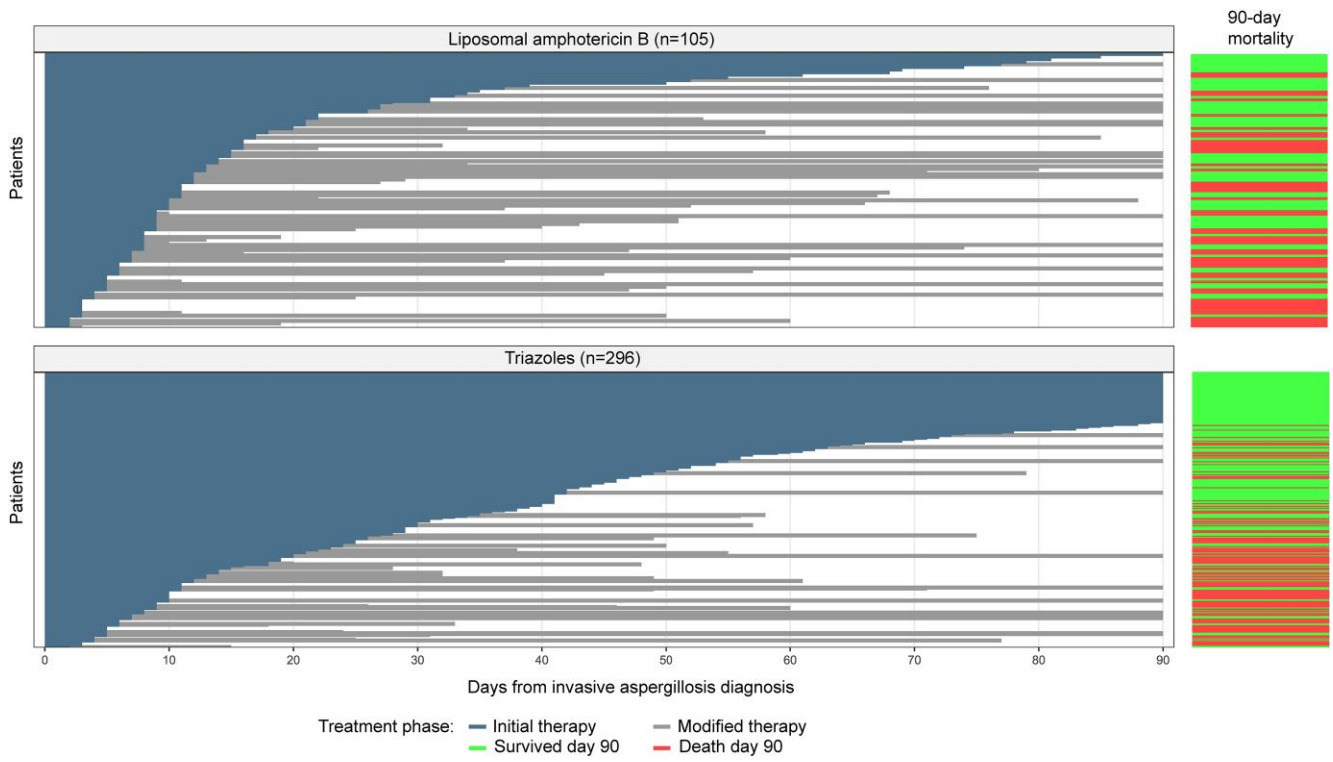

Figure 1. Treatment trajectories and 90-day outcomes in invasive aspergillosis. Swimlane plot showing individual patient treatment courses from diagnosis to 90 days or death. Lines represent patients (bluish-gray: initial therapy; light blue: postmodification), ordered by modification timing. Adjacent heatmap shows 90-day survival (green: alive; red: deceased). Of 296 triazole patients, 46 (15.5%) modified treatment (median 13 d) with 41.2% mortality. Of 105 L-AmB patients, 66 (62.9%) switched therapy (median 10 d) with 46.7% mortality. L-AmB, liposomal amphotericin B.

hazards assumption (Supplementary Figure 9). Sensitivity analysis for unmeasured confounding in the association between L-AmB and 90-day mortality compared to triazole therapy was performed (Supplementary Figure 10) and revealed an E-value for the L-AmB point estimate and for the CI of 2.21 and 1.31, respectively, indicating moderate sensitivity to unmeasured confounding. Hence, an unmeasured confounder associated with both initial L-AmB use and 90-day mortality by a risk ratio of ∼2.2 each could explain the point estimate.

DISCUSSION

This multicenter study involving a large cohort of patients with proven or probable invasive aspergillosis found that initial L-AmB therapy was associated with a numerically higher but statistically nonsignificant 90-day mortality compared to triazole therapy after adjustment for confounding, although L-AmB was used initially in more high-risk patients. The overall 90-day mortality of 42.6% confirms the persistent high burden of IA, with mortality ranging from 30% in SOT recipients to 54% in patients with VAPA.

Our findings align with contemporary cohorts reporting 12-week mortality rates of 30%–43%, though recent data from Australia and New Zealand suggest improving outcomes with modern management strategies [23]. Notably, VAPA emerged as the second most common predisposing condition with the highest associated mortality, highlighting an evolving epidemiological pattern not captured in earlier studies. Hematological malignancy remained the predominant risk factor, whereas ICU-acquired IA carried a 2-fold increased mortality risk, consistent with previous reports [2, 24].

The comparable effectiveness of L-AmB and triazoles in our adjusted analysis contrasts with the established superiority of voriconazole over amphotericin B deoxycholate from randomized trials. However, no prospective comparisons exist between triazoles and L-AmB. Importantly, L-AmB was preferentially used in higher risk patients—65.8% had hematological malignancies and 58.1% had received prior azole prophylaxis, representing breakthrough infections associated with inherently worse outcomes. This channeling bias, whereby sicker patients receive L-AmB, underscores the importance of our IPTW-adjusted landmark analysis to minimize confounding by indication and immortal time bias.

Treatment patterns differed notably between groups: L-AmB discontinuation primarily reflected planned transitions to oral therapy, while triazole changes were driven by adverse events

Table 2. Comparison Between Survivors and Nonsurvivors at 90-Day Within IA Diagnosis

	Survivors N = 230 (57.4%)	Nonsurvivors N = 171 (42.6%)
Enrolling center		
Center A	168 (73.0)	120 (70.2)
Center B	62 (27.0)	51 (29.8)
Demographic data		
Age (years) [median (IQR)]	63 (53–71)	68 (59–76)
Sex, male	134 (58.3)	110 (64.3)
Charlson comorbidity index (median, IQR)	4 (3–6)	5 (3–7)
Risk factors		
SOT	37 (16.1)	16 (9.4)
Liver	15 (40.5)	5 (31.3)
Kidney	0 (0)	3 (18.8)
Lung	12 (21.6)	3 (18.8)
Heart	8 (21.6)	5 (31.3)
Hematologic malignancies	92 (40.4)	58 (33.9)
HSCT	37 (16.1)	16 (9.4)
AML	39 (17.0)	23 (13.5)
CLL	4 (1.7)	3 (1.8)
ALL	6 (2.6)	3 (1.8)
MM	8 (3.5)	6 (3.5)
Lymphoma	34 (14.8)	21 (12.3)
Neutropenia	33 (14.3)	20 (11.7)
Solid tumor	23 (10.0)	27 (15.8)
Chronic steroid treatment	39 (17.0)	25 (14.6)
COPD	35 (15.2)	29 (17.0)
ICU stay >14 d	18 (7.8)	19 (11.1)
Recent major surgery	15 (6.5)	7 (4.1)
Concomitant viral infection (VAPA)	55 (23.9)	65 (38.0)
Antifungal prophylaxis at diagnosis	73 (31.7)	41 (24.0)
Ward of IA diagnosis		
Medical ward	182 (79.1)	109 (63.7)
ICU	48 (20.9)	62 (36.3)
Diagnosis classification		
Proven	11 (4.8)	5 (2.9)
Probable	219 (95.2)	166 (97.1)
Microbiological features		
Number of cultures performed	164 (71.3)	137 (80.1)
Any positive culture	78 (47.6)	70 (51.1)
Aspergillus isolation		
A. fumigatus	44 (21.4)	55 (28.2)
A. flavus	20 (9.7)	10 (5.1)
A. niger	5 (2.4)	6 (3.1)
A. terreus	5 (2.4)	5 (2.6)
A. nidulans	1 (0.5)	1 (0.5)
Number of PCR performed	38 (16.5)	23 (13.5)
PCR positive	26 (68.4)	17 (73.9)
Median value (cp/mL, IQR)	3498 (809–6150)	3498 (642–13 854)
Number of GM on BAL performed	201 (87.4)	160 (93.6)
GM ≥1 on BAL	186 (92.5)	147 (91.9)
Median value (ODI, IQR)	3.6 (2.0–5.0)	3.6 (2.1–4.9)
Number of serum GM performed	123 (53.5)	84 (49.1)
GM ≥0.5 on serum	44 (35.8)	43 (51.2)
Median value (ODI, IQR)	1.2 (0.8–2.1)	1.5 (0.8–3.8)
Site of diagnosis		
Isolated pulmonary	192 (93.2)	173 (88.7)
Disseminated	9 (4.4)	20 (10.3)
Radiological findings		
Nodules	116 (56.3)	85 (43.6)

Table 2. Continued

	Survivors N = 230 (57.4%)	Nonsurvivors N = 171 (42.6%)
Ground-glass opacity	124 (60.2)	113 (57.9)
Halo sign	26 (12.6)	21 (10.8)
Air crescent sign	3 (1.5)	3 (1.5)
Consolidation	111 (53.9)	120 (61.5)
Cavity	36 (17.5)	27 (13.8)
Pleural effusion	31 (15.0)	43 (22.1)
Antifungal treatment		
Voriconazole	159 (69.1)	113 (66.1)
First voriconazole TDM (mg/mL) (median, IQR)	3.2 (1.5–5.2)	3.9 (1.9–5.6)
Second voriconazole TDM (mg/mL) (median, IQR)	3.4 (1.6–5.2)	4.9 (2.6–7.6)
L-AmB	56 (24.3)	49 (28.7)
3 mg/kg/daily	32 (65.3)	44 (81.5)
5 mg/kg/daily	17 (34.7)	10 (18.5)
Isavuconazole	15 (6.5)	9 (5.3)
Combination treatment	11 (4.8)	7 (4.1)
Time to IA diagnosis to antifungal start (days) (median)	0 (0–2)	0 (0–3)
Shift to another antifungal	80 (34.8)	38 (22.2)
Voriconazole	26 (32.5)	16 (42.1)
Isavuconazole	31 (38.8)	16 (42.1)
L-AmB	19 (23.8)	5 (13.2)
Posaconazole	4 (5.0)	1 (2.6)
Days from antifungal start to shift (median)	12 (8–28)	9 (7–15)
Overall antifungal treatment (days) (median, IQR)	71 (42–125)	19 (9–39)
Clinical outcome 30-day (N = 375)		
Complete symptoms resolutions	58 (25.6)	7 (4.7)
Partial symptoms resolutions	136 (59.9)	37 (25.0)
No symptoms resolutions	28 (12.3)	56 (37.8)
Worsening of symptoms	5 (2.2)	48 (32.4)
Radiological outcome 30-day (N = 385)		
Complete resolution	34 (14.9)	7 (4.5)
>25% resolution	119 (52.2)	18 (11.5)
<25% resolution	35 (15.4)	18 (11.5)
Progression	22 (0.9)	1 (0.6)
Microbiological outcome 30-day (N = 77)		
Negative GM	40 (17.4)	19 (11.1)
Reduction GM	11 (4.8)	6 (3.5)
Clinical outcome 90-day (N = 252)		
Complete symptoms resolutions	158 (72.8)	9 (25.7)
Partial symptoms resolutions	42 (19.4)	5 (14.3)
No symptoms resolutions	11 (5.1)	11 (31.4)
Worsening of symptoms	6 (2.8)	10 (28.6)
Radiological outcome 90-day (N = 259)		
Complete resolution	87 (40.1)	4 (9.5)
>25% resolution	54 (24.9)	4 (9.5)
<25% resolution	15 (6.9)	5 (11.9)
Progression	22 (10.1)	7 (16.7)
Length of ICU stay (days) (median, IQR)	26 (11–47)	20 (11–35)
Length of hospital stay (days) (median, IQR)	44 (25–66)	32 (18–47)

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; BAL, bronchoalveolar lavage; CLL, Chronic Lymphocytic Leukemia; COPD, chronic obstructive pulmonary disease; GM, galactomannan; HCT, Hematopoietic Cell Transplantation; HSCT, hematopoietic stem cell transplant; IA, invasive aspergillosis; ICU, intensive care unit; IQR, interquartile range; L-AmB, liposomal amphotericin B; MM, Multiple Myeloma; ODI, Optical Density Index; PCR, polymerase chain reaction; SOT, solid organ transplantation; TDM, Therapeutic Drug Monitoring; VAPA, viral-associated pulmonary aspergillosis.

or treatment failure. This confirms that L-AmB treatment often serves effectively as initial stabilization therapy before oral step-down, particularly in breakthrough infections where azole resistance is suspected.

A. fumigatus remained the predominant pathogen, though *A. flavus*—with intrinsically reduced L-AmB susceptibility—emerged as an important cause [25]. While antifungal susceptibility testing was limited (available in <50% of culture-positive

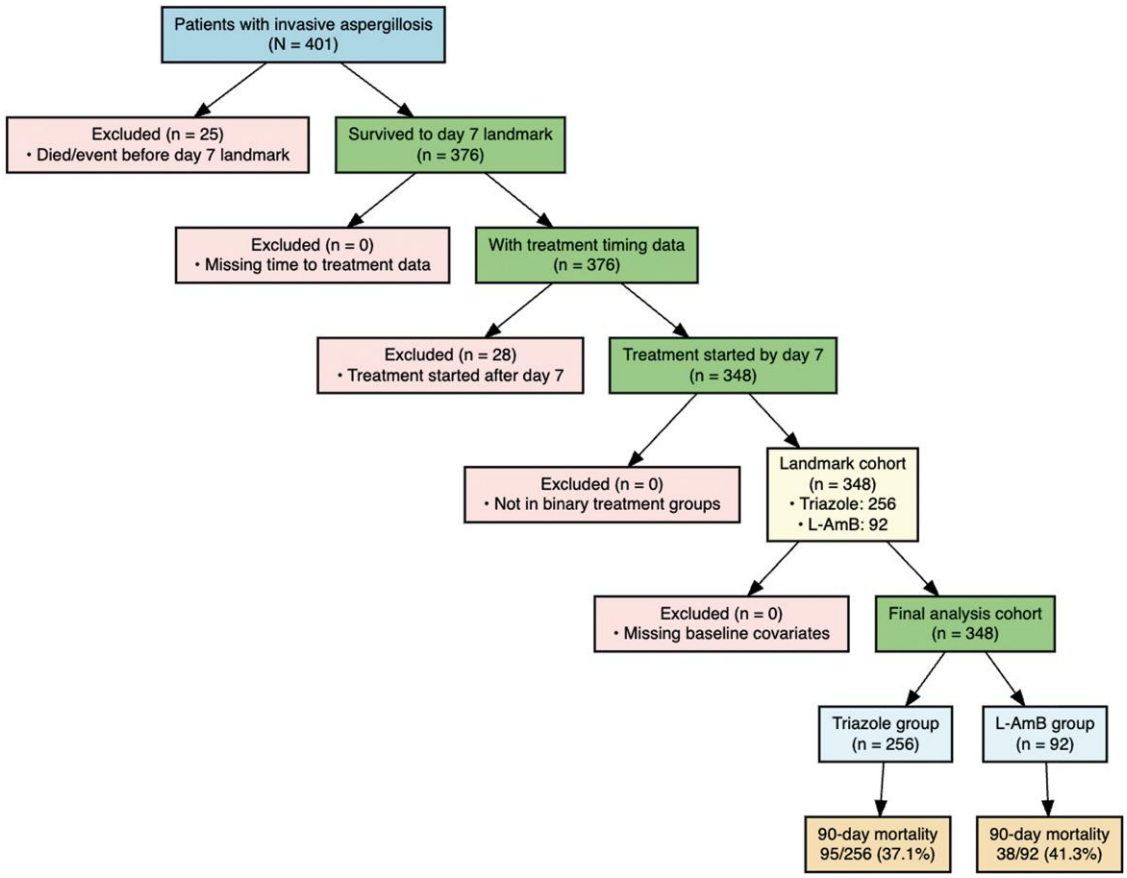

Figure 2. CONSORT diagram of patients included in the analysis.

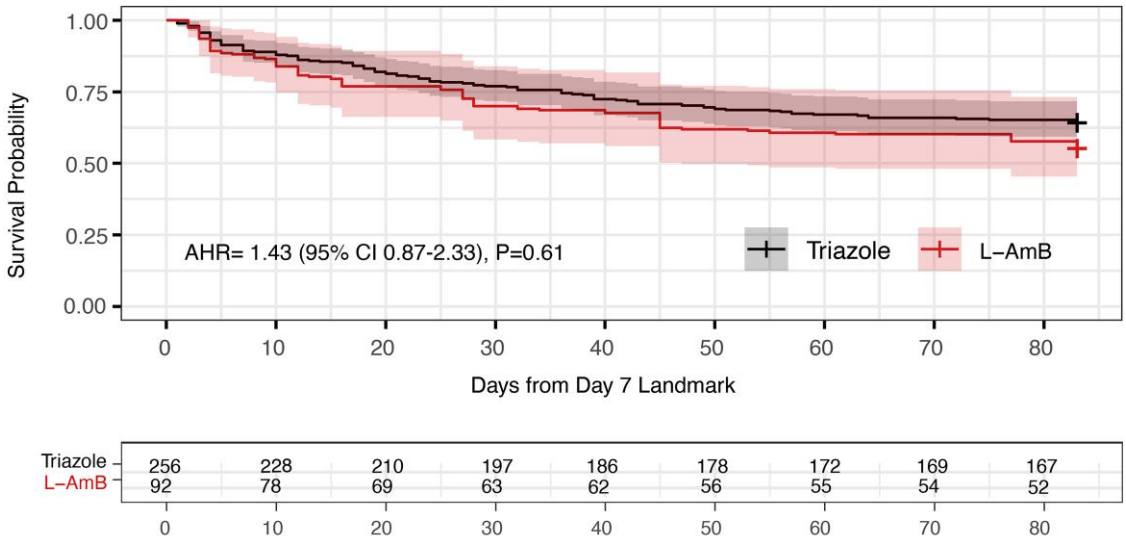

Figure 3. Kaplan–Meier curves of 90-day survival after inverse probability of treatment weighting (IPTW) comparing triazoles (black, n = 256) and liposomal amphotericin B (L-AmB, red, n = 92). The analysis included patients alive at the day-7 landmark who initiated antifungal therapy within 7 d of diagnosis. Stabilized weights were estimated from baseline covariates (hematologic malignancy, chronic steroid use, hepatic dysfunction, and antifungal prophylaxis). Time zero represents day 7; shaded areas denote 95% confidence intervals (CI). The adjusted hazard ratio was 1.43 (95% CI, .87–2.33; $P = .61$), indicating no significant difference in mortality. Weighted numbers at risk are shown below the curves; censoring events are indicated by vertical ticks.

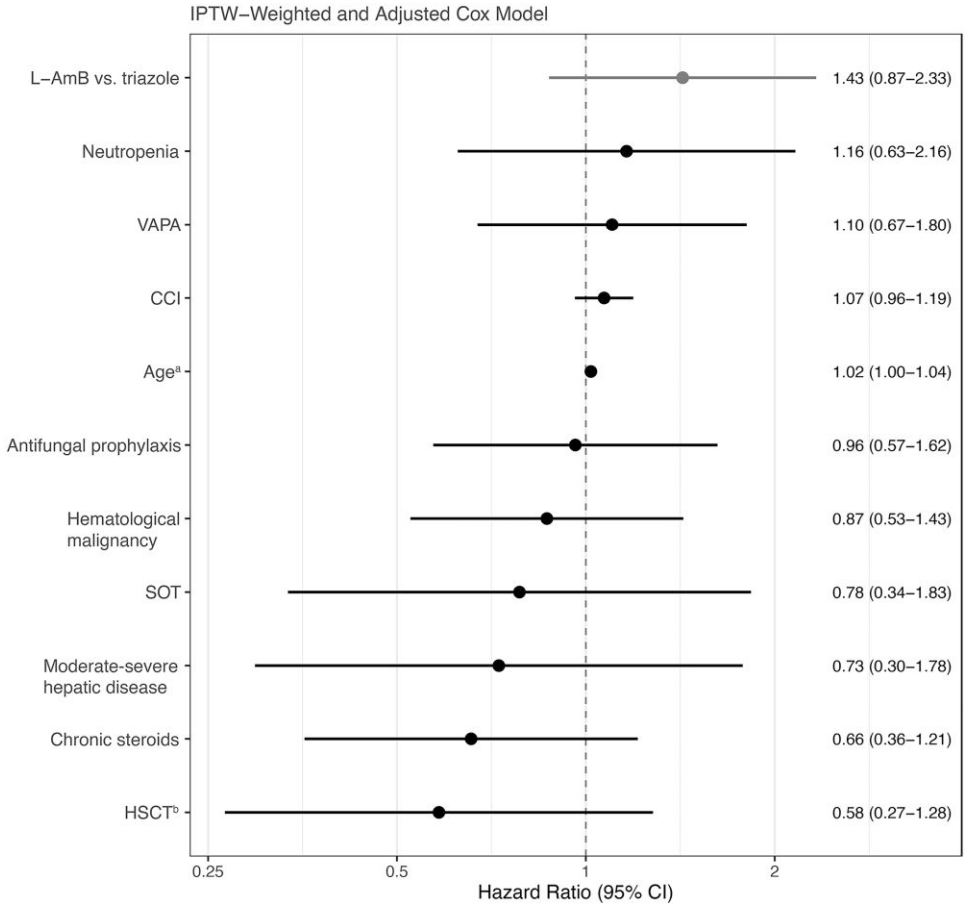

Figure 4. Forest plot of hazard ratios (HRs) with 95% confidence intervals (CIs) for 90-day mortality from the day 7 landmark, using a regression model with IPTW and covariate adjustment. The dashed line at HR = 1.0 indicates no effect; squares denote point estimates, and horizontal lines the 95% CI. Variables included: treatment group (L-AmB vs triazole [reference]), age, Charlson Comorbidity Index (CCI), ventilator-associated pulmonary aspergillosis (VAPA), neutropenia, hematopoietic stem cell transplant (HSCT), chronic steroid use, hepatic dysfunction, solid organ transplant (SOT), hematologic malignancy, and antifungal prophylaxis. L-AmB was associated with a nonsignificant 43% higher mortality versus triazole (HR 1.43; 95% CI, .87–2.33). Gray shading highlights the treatment effect. HR >1 indicates increased mortality risk; HR <1 indicates protection. [a]Per 10-year increase. [b]Per unit increase. IPTW, inverse probability of treatment weighting; L-AmB, liposomal amphotericin B.

cases), Italian surveillance data indicate low triazole resistance rates (~6%), suggesting our findings are generalizable to settings with similar resistance epidemiology [26].

Despite robust adjustment for measured confounders and satisfactory model diagnostics, residual confounding from unmeasured severity of illness indicators at the time of IA diagnosis (elevated galactomannan, organ dysfunction scores) may persist. Additionally, the standard L-AmB dose of 3 mg/kg/day used in most patients may be suboptimal in critically ill patients with altered pharmacokinetics, as suggested by the recent SAFE-ICU study [27], particularly given the limited availability of therapeutic drug monitoring to guide dosing, which is commonly used for triazoles. The landmark IPTW analysis, although addressing immortal time bias and confounding by indication, excluded 53 early deaths, potentially underestimating treatment differences. However, with 133 postlandmark events, statistical power remained adequate. The retrospective design limits causal inference, though our dual-center approach reduces single-institution bias.

In conclusion, our contemporary cohort study demonstrated that initial therapy with L-AmB and triazole therapy demonstrated comparable 90-day mortality for IA. These results should be interpreted as associations in the context of possible residual confounding and require confirmation, and support individualized treatment selection based on patient factors, prior antifungal exposure, and local resistance patterns rather than presumed superiority of either agent. Future studies should evaluate the impact of empiric antifungal selection on outcomes, as L-AmB's broader spectrum (covering both *Aspergillus* and Mucorales) may confer unmeasured survival benefits compared to triazoles in high-risk patients where definitive fungal identification is pending. Additionally, incorporating prediagnosis empiric therapy exposure as a covariate would better capture the complex treatment trajectories that

influence mortality in invasive fungal infections beyond IA alone. Prospective trials comparing L-AmB with modern triazoles remain needed to definitively establish optimal first-line therapy.

Supplementary Data

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

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