

RESEARCH LETTER

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Inhaled liposomal amphotericin-B as a prophylactic treatment for COVID-19-associated pulmonary aspergillosis/aspergillus tracheobronchitis

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COVID-19-associated pulmonary aspergillosis (CAPA) is a recently described complication of severe Coronavirus Disease of 2019 and is associated with increased morbidity and mortality [1, 2]. Also *Aspergillus tracheobronchitis* (AT) is common in this disease. We reported already during the first pandemic wave that CAPA/AT was frequently encountered in our 31-bed mixed ICU (ZiekenhuisNetwerk Antwerpen, Belgium) where we often take care of comorbid and immunocompromized patients, regularly of low socioeconomic status [3]. Since we were dealing with a novel disease and in view of the extensively documented health risks of influenza-associated pulmonary aspergillosis, we decided a few months after the beginning of the pandemic to start with a routine off-label prophylactic regimen in mechanically ventilated patients [4]. We chose inhaled liposomal amphotericin-B in view of its successful and safe use in hematological disease and in solid organ transplant patients [5]. We chose it over prophylactic triazoles to minimize the risk of azole resistance and in view of local reimbursement criteria. Specifically, 12.5 mg Ambisome[®] (Gilead Sciences,

Inc.), dissolved in 3 mL of sterile water with the addition of 5 drops of salbutamol, was nebulized on Mondays and Thursdays using our routine Covidien[®] DAR[®] nebulizer set in all intubated patients. The solution was administered as close as possible to the endotracheal tube to avoid precipitate in the circuit. After the nebulization, the expiratory filter was checked for potential clogging.

We performed this retrospective observational study to assess the effectiveness of this prophylactic regimen. We aimed to compare the proportion of patients who protracted proven or probable CAPA/AT while receiving the treatment with the proportion of patients with CAPA/AT who only received standard of care. We also assessed the proportion of patients with *Aspergillus* colonization in endotracheal aspirates in relation to the treatment. The study was approved by our Institutional Review Board (approval nr. 5530) with waiving of patient consent. We included every patient who had been mechanically ventilated for COVID-19 pneumonia and had undergone a diagnostic procedure for CAPA/AT between the start of the first pandemic

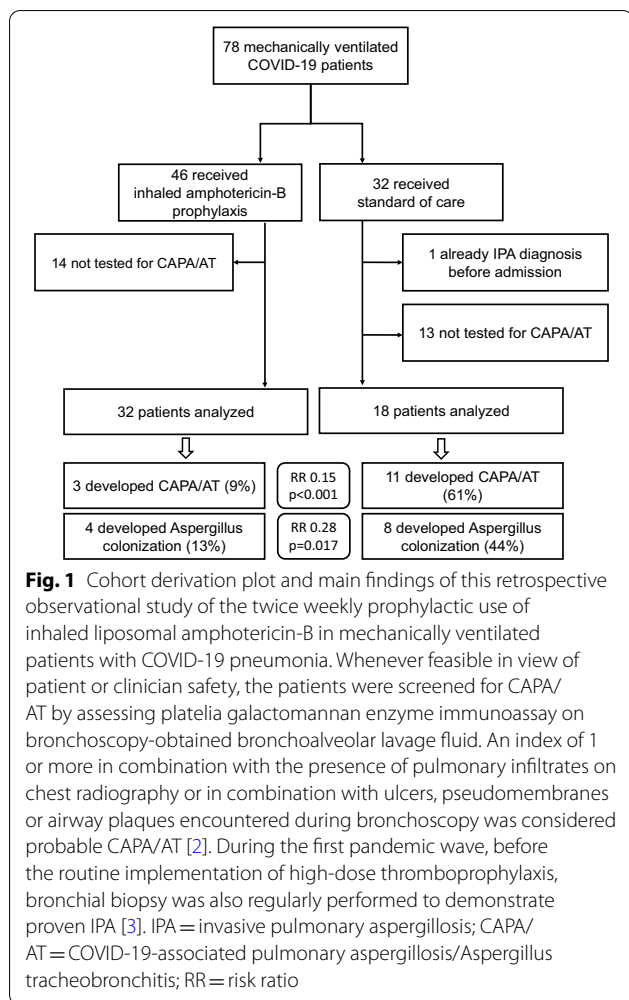
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wave until March 31, 2021. Patients who protracted invasive pulmonary aspergillosis before ICU admission were excluded. The routine implementation of the

prophylactic regimen made this mostly a before and after study, although a few patients did not receive the treatment after its implementation and were analyzed in the standard-of-care group.

During the study period, 203 patients were admitted to our ICU for COVID-19 pneumonia of which 78 needed mechanical ventilation. Not every patient was screened for CAPA/AT: especially in the early phase of the pandemic, physicians were reluctant to perform aerosol-generating diagnostic procedures. In other cases, oxygen need was considered too high to allow a safe procedure. Figure 1 shows the derivation of the study cohort of eventually 50 patients. The patient characteristics are reported in Table 1. Eleven patients who received the standard of care developed CAPA/AT, compared to three of the patients who did receive the prophylactic treatment (risk ratio (RR) was 0.15, 95%CI 0.05 to 0.48; $\text{Chi}^2 p < 0.001$). Median time to diagnosis was 11 days in the treated group (IQR 7–19) and 12 days in the untreated group (IQR 8–18) ($p = 0.74$). Also the proportion of Aspergillus colonization in endotracheal aspirates was significantly lower: 44% ($n = 8$) in the standard of care group compared to 13% ($n = 4$) in the treated group (RR 0.28, 95%CI 0.10 to 0.81; Fisher’s exact $p = 0.017$). No treatment-related adverse events were encountered, including bronchospasms that urged to stop the prophylaxis.

In this observational study, we found that a twice weekly prophylactic regimen of 12.5 mg inhaled liposomal amphotericin-B reduced the incidence of CAPA/AT in mechanically ventilated COVID-19 patients. Confirmation of these findings in a randomized clinical trial is needed.

Table 1 Characteristics of the study cohort

	Overall (n = 50)	Standard of care (n = 18)	Inhaled amphotericin-B (n = 32)	p-value
<i>Baseline characteristics</i>				
Age	65.5 (10.8)	64.8 (13.0)	65.9 (9.62)	0.75 ^a
Male sex	37 (74.0%)	17 (94.4%)	20 (62.5%)	0.02 ^b
Immunocompromized state	15 (30.0%)	7 (38.9%)	8 (25.0%)	0.30 ^c
Cancer (incl. hematological)	13 (26.0%)	5 (27.8%)	8 (25.0%)	
Immunosuppressive or HIV medication	6 (12.0%)	2 (11.1%)	4 (12.5%)	
Organ transplant	1 (2.0%)	0 (0%)	1 (3.1%)	
Primary immunoglobulin G deficiency	2 (4.0%)	2 (11.1%)	0 (0%)	
<i>Other comorbidities</i>				
Diabetes mellitus	26 (52.0%)	8 (44.4%)	18 (56.2%)	0.42 ^c
Arterial hypertension	26 (52%)	6 (33.3%)	20 (62.5%)	0.02 ^c
Heart failure (NYHA ≥ 2)	2 (4.4%)	1 (5.6%)	1 (3.1%)	1 ^b
Chronic kidney disease without dialysis	5 (10%)	2 (11.1%)	3 (9.4%)	1 ^b
Chronic dialysis	3 (6%)	1 (5.6%)	2 (6.3%)	1 ^b
Modified frailty index [6]	0.16 (0.12)	0.12 (0.11)	0.18 (0.13)	0.14 ^a
<i>Admission characteristics</i>				
PaO ₂ /FiO ₂ at admission	111 (76–136)	91 (73–147)	113 (81–136)	0.41 ^d
SOFA score at admission	5.5 (4–8)	7 (4–8)	5 (4–8)	0.51 ^d
SAPS-3 score	55.7 (17.7)	54.0 (12.0)	54.6 (14.1)	0.68 ^a
Time from hospital admission to intubation (days)	3.5 (1–10)	5.5 (1–16)	3 (1–10)	0.51 ^d
Time from ICU admission to intubation (days)	2 (0–7)	1.5 (0–8)	2 (0–5)	0.67 ^d
Vasopressor use	48 (96%)	16 (88.9%)	32 (100%)	0.05 ^c
Renal replacement therapy (incl. chronic dialysis)	20 (40%)	9 (50.0%)	11 (34.4%)	0.28 ^c
<i>COVID-19 treatment</i>				
Dexamethasone	33 (66.0%)	9 (50.0%)	24 (75.0%)	0.07 ^c
Tocilizumab	8 (16.0%)	2 (11.1%)	6 (18.8%)	0.69 ^b

Numbers are presented as means (standard deviation), n (%) or medians (interquartile range) as appropriate. Test statistics: a = independent samples t-test; b = Fisher's exact test; c = Chi square test; d = Mann-Whitney test

NYHA = New York Heart Association; SAPS = simplified acute physiology score; SOFA = sequential organ assessment score; ICU = intensive care unit; COVID-19 = Coronavirus Disease of 2019

Acknowledgements

We thank Gilead Sciences, Belgium for providing us with Ambisome[®] as medical samples.

Authors' contributions

SVA collected the data and co-wrote the first draft of the manuscript; KD collected the data on the treatment under study; ER supervised the statistical analysis; NVR conceptualized the study with input from LR and JW, co-wrote the first draft of the manuscript and performed the statistical analysis. LR and JW contributed to revisions. All authors read and approved the final manuscript.

Funding

No funds were received for the current work.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Waiving of informed consent (Institutional Review Board Ziekenhuisnetwerk Antwerpen, Approval nr. 5530). Statement is included in the manuscript.

Consent for publication

N/A.

Competing interests

The authors declare that they have no conflict of interest.

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Received: 26 July 2021 Accepted: 9 August 2021

Published online: 19 August 2021

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