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ORIGINAL RESEARCH

Candida auris Candidemia in Critically Ill, Colonized Patients: Cumulative Incidence and Risk Factors

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ABSTRACT

Introduction: *Candida auris* (*C. auris*) is an emerging nosocomial pathogen, and a sharp rise in cases of colonization and infection has been registered in intensive care units (ICUs) during the ongoing coronavirus disease 2019 (COVID-19) pandemic. The unfavorable resistance profile of *C. auris* and the potential high mortality of *C. auris* infections represent an important challenge for physicians.

Methods: We conducted a single-center retrospective study including all patients admitted to ICUs with isolation of *C. auris* in any non-sterile body site between February 20, 2020, and May 31, 2021. The primary aim of the study was to assess the cumulative incidence of *C. auris* candidemia in colonized patients. The secondary aim was to identify predictors of *C. auris* candidemia in the study population.

Results: During the study period, 157 patients admitted to ICUs in our hospital became colonized with *C. auris*; 59% of them were affected by COVID-19. Overall, 27 patients (17%) developed *C. auris* candidemia. The cumulative risk of developing *C. auris* candidemia was > 25% at 60 days after first detection of *C. auris* colonization. Seven patients with *C. auris* candidemia (26%) also developed a late recurrent episode. All *C. auris* blood isolates during the first occurring episode were resistant to fluconazole and susceptible to echinocandins,

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while 15 (56%) were resistant to amphotericin B. During late recurrent episodes, emergent resistance to caspofungin and amphotericin B occurred in one case each. In the final multivariable model, only multisite colonization retained an independent association with the development of *C. auris* candidemia.
Conclusion: *Candida auris* candidemia may occur in up to one fourth of colonized critically ill patients, and multisite colonization is an independent risk factor for the development of candidemia. Implementing adequate infection control measures remains crucial to prevent colonization with *C. auris* and indirectly the subsequent development of infection.

Keywords: *Candida auris*; Candidemia; Candidiasis; Colonization; ICU

Key Summary Points

Candida auris (*C. auris*) is an emergent pathogen causing nosocomial outbreaks at a global scale, especially in intensive care units.

Identifying predictors of *C. auris* candidemia could improve early diagnosis and prognosis.

In our cohort of critically ill colonized patients, the cumulative risk of developing *C. auris* candidemia exceeded 25% at 60 days after detection of colonization.

High crude mortality was registered in episodes of late recurrent *C. auris* candidemia.

Multisite *C. auris* colonization was associated with the development of *C. auris* candidemia in our population.

INTRODUCTION

Candida auris is a yeast isolated for the first time in 2009 from the ear canal of a patient in Japan [1]. Since then, due to its persistence in the hospital environment and ease of transmission, it has caused numerous healthcare-associated outbreaks, described in six continents [2]. Recently, a sharp rise in new cases of colonization and infection has been reported, especially during the ongoing coronavirus disease 2019 (COVID-19) pandemic [3, 4]. These outbreaks involved mainly intensive care units (ICUs) [5].

One of the major challenges posed by *C. auris* is its unfavorable profile of resistance to antifungal agents, with > 90% of strains being resistant to fluconazole, 35% to amphotericin B, and over 40% expressing combined resistance to two or more classes of antifungals [6]. This characteristic may complicate the management of invasive *C. auris* infections such as candidemia, potentially contributing to high mortality [7, 8]. *C. auris* candidemia usually follows colonization; thus, understanding who among colonized patients is at higher risk of developing candidemia may help in improving early diagnosis, and also prevent invasive infection through interventions on modifiable predictors.

The aims of the present single-center study were to assess the cumulative incidence of *C. auris* candidemia and to identify predictors of *C. auris* candidemia in colonized patients admitted to the ICU.

METHODS

Study Design and Setting

This is a retrospective, single-center study conducted at San Martino Policlinico Hospital, a 1200-bed teaching hospital in Genoa, Northern Italy, during the period from February 20, 2020, to May 31, 2021. All adult patients admitted to

any ICU of our hospital and with isolation of *C. auris* from non-sterile body sites (skin, urine, and/or respiratory tract specimens) were included in the study. The study was approved by the Ethics Committee of the Liguria region (N. CER Liguria 31/2022).

Our hospital has five ICUs: (i) one with 12 beds dedicated to cardiovascular surgical patients; (ii) one with 10 beds dedicated to surgical and solid organ transplant patients; (iii) one with 10 beds dedicated to COVID-19 and respiratory patients; (iv) the largest one with 28 beds for neurosurgical and general ICU patients, which was in part converted to care for COVID-19 patients during the peak of cases in our region; (v) one with 8 beds in the emergency department, also caring for COVID-19 patients when needed for epidemiological reasons. During the whole study period, a dedicated team of infectious diseases specialists provided daily consultations in all the above-cited ICUs, to improve the management of infectious complications in critically ill patients.

Objectives

The primary objective of our study was to describe the cumulative incidence of *C. auris* candidemia among critically ill patients colonized by *C. auris*. The secondary objective was to assess independent predictors of *C. auris* candidemia in critically ill, colonized patients.

Definitions and Protocols

Colonization with *C. auris* was defined by the isolation of *C. auris* from at least one non-sterile site (urine, skin, and/or respiratory tract specimens), in the absence of clinical signs or symptoms of infection. Multisite colonization was defined as isolation of *C. auris* from more than one non-sterile site. Candidemia was defined by the isolation of *C. auris* from at least one blood culture. A late recurrent episode of *C. auris* candidemia was defined as new blood culture positivity after 30 days from the resolution of a previous episode [9]. Blood cultures were collected upon clinical suspicion of invasive infection from caring clinicians.

In order to contain *C. auris* dissemination in our hospital [10], an internal infection control protocol was implemented. It can be summarized as follows: (i) screening for skin colonization (combined axilla and groin skin swab) at admission to the ICU for early identification of possible community-acquired cases; (ii) repeated weekly screening for skin colonization during ICU admission until first detection of *C. auris* colonization; (iii) implementation of strict contact precautions for colonized patients; (iv) environmental intervention bundle to reduce the *C. auris* burden; (v) screening for skin colonization upon *C. auris*-negative patients' discharge from the ICU and admission to a different ward, with preventive contact precautions pending culture results. Moreover, per center protocol, all patients admitted to the ICUs of our hospital during the study period underwent weekly culture of deep respiratory samples (whenever mechanically ventilated) and urine culture.

Microbiological Analysis

Candida auris was identified in clinical and screening specimens with matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS—VITEK MS; bioMérieux, Marcy-l'Etoile, France) using VITEK MS v4.0 software. Antifungal susceptibility testing (AFST) was carried out according to the Clinical and Laboratory Standards Institute microdilution method using the Sensititre YeastOne panel (Thermo Scientific, Waltham, MA, USA); minimum inhibitory concentration (MIC) values were determined for azoles, echinocandins, and amphotericin B. Since no species-specific susceptibility breakpoints are currently available for *C. auris*, AFST results were interpreted according to the tentative breakpoints proposed by the US Centers for Disease Control and Prevention [11].

Data Collected for the Analysis

The following information was collected from electronic medical records as they were at the time of detection of *C. auris* colonization: age in

years; gender; Charlson comorbidity index [12]; history of diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2), previous myocardial infarction, human immunodeficiency virus (HIV) infection, solid cancer, hematological malignancy, solid organ transplant (SOT), hematopoietic stem cell transplantation (HSCT); admission from long-term care facilities (LTCF); previous hospitalization (within 6 months); previous abdominal surgery (within 30 days); previous therapies (within 30 days) with antibiotics, antifungals (azoles and/or echinocandins and/or polyenes), steroids or other immunomodulatory agents; previous ICU stay in days before *C. auris* colonization; absolute neutrophil count (ANC) < 500 cell/mm^3; infection by SARS-CoV-2 defined as a positive real-time polymerase chain reaction (RT-PCR) in at least one respiratory specimen; invasive mechanical ventilation; continuous renal replacement therapy (CRRT); extracorporeal membrane oxygenation (ECMO); total parenteral nutrition (TPN); presence of central venous catheter (CVC). Susceptibility test results for *C. auris* blood isolates and crude 30-day mortality after the first positive culture in candidemia episodes were also collected.

Statistical Analysis

No a priori sample size calculations were performed for this exploratory study. For the primary descriptive analysis, the cumulative risk of *C. auris* candidemia in colonized ICU patients was obtained by means of the Aalen–Johansen method, considering the first occurring *C. auris* candidemia as the event of interest, death as a competing event, and discharge from the ICU as a right-censoring event [13]. The time of origin was set at the day colonization by *C. auris* was first detected in the ICU (or equal to ICU admission in the case of already colonized patients), with the maximum length of follow-up being 60 days after the time of origin.

To describe the demographic and clinical characteristics of the study population, categorical variables were summarized with numbers and percentages, and continuous variables with median and interquartile range. The 95% confidence interval (CI) was calculated for both categorical and continuous estimates [14, 15]. For the secondary exploratory analysis of predictors of *C. auris* candidemia in colonized ICU patients, the possible association between demographic/clinical variables and the first occurring *C. auris* candidemia episode was first tested in univariable Cox regression models for providing unadjusted cause-specific hazard ratios (HR) with their 95% CI, after having verified proportionality of hazards with the Schoenfeld residuals-based test implemented in the R survival library. Then, variables potentially associated with the development of *C. auris* candidemia in univariable comparisons ($p < 0.10$) were included in an initial Cox regression multivariable model, and further selected for the final multivariable model through a stepwise backward procedure based on the Akaike information criterion, to provide adjusted cause-specific HR. Statistical analyses were performed using the R Statistical Software program (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 157 patients admitted to the ICU of our hospital became colonized with *C. auris*. Seventy-one percent ($n = 111$) were male, with a median age of 64 years (interquartile range [IQR] 58–71). Patients with COVID-19 accounted for 59% of the study population (92/157). The complete demographic and clinical characteristics of the study population are reported in Table 1. All patients had a CVC (157/157, 100%), and the majority had received previous antibiotic therapy (152/157, 97%) and were mechanically ventilated (150/157, 96%).

Overall, 27/157 (17%) patients developed at least one episode of *C. auris* candidemia, after a median of 29 days (IQR 15–38) from the first detection of colonization. The cumulative risk of developing at least one episode of *C. auris* candidemia exceeded 25% at 60 days after

Table 1 Characteristics of ICU patients with *Candida auris* colonization

Variable	No. of patients (%)[a] (Total = 157)	95% CI for proportions and medians
Demographic variables		
Age in years, median (IQR)	64 (58–71)	62–66
Male gender	111 (71)	63–78
Medical history		
Charlson score, median (IQR)	3 (2–4)	2–3
Diabetes mellitus	36 (23)	17–30
Chronic obstructive pulmonary disease	32 (20)	14–27
Chronic kidney disease	7 (4)	2–9
Previous myocardial infarction	18 (11)	7–17
HIV infection	0 (0)	0–2
Solid cancer	11 (7)	4–12
Hematological malignancy	6 (4)	2–8
Solid organ transplant	4 (3)	1–6
Hematopoietic stem cell transplantation	1 (1)	0–3
Admission from LTCF	1 (1)	0–3
Previous hospitalization (within 6 months)	11 (7)	4–12
Previous abdominal surgery (within 30 days)	19 (12)	8–18
Previous therapy (within 30 days prior to colonization)[b]		
Previous antibiotics	152 (97)	93–99
Previous beta-lactams	150 (96)	91–98
Previous fluoroquinolones	16 (10)	6–16
Previous antifungals	61 (39)	31–47
Previous azoles	8 (5)	2–10
Previous polyenes	4 (3)	1–6
Previous echinocandins	60 (38)	31–46
Previous steroids	116 (74)	66–80
Previous immunomodulatory agents	17 (11)	7–17
Other collected variables		
Previous ICU stay in days, median (IQR)	14 (8–23)	12–17
Neutropenia (ANC < 500 cell/mm^3)	2 (1)	(0–5)
COVID-19	92 (59)	(51–66)
Invasive mechanical ventilation	150 (96)	(91–98)

Table 1 continued

Variable	No. of patients (%)[a](Total = 157)	95% CI for proportions and medians
Continuous renal replacement therapy	63 (40)	(33–48)
Extracorporeal membrane oxygenation	2 (1)	(0–5)
Presence of CVC	157 (100)	(98–100)
Total parenteral nutrition	74 (47)	(39–55)
Site of *C. auris* colonization[b]		
Skin colonization	146 (93)	88–96
Urinary colonization	38 (24)	18–31
Respiratory colonization	77 (49)	41–57
Multisite colonization	78 (50)	42–58

ANC absolute neutrophil count, *COVID-19* coronavirus disease 2019, *CI* confidence intervals, *CVC* central venous catheter, *HIV* human immunodficiency virus, *ICU* intensive care unit, *IQR* interquartile range, *LTCF* long-term care facility
[a]Results are presented as no. of patients (%) unless otherwise indicated
[b]Not mutually exclusive

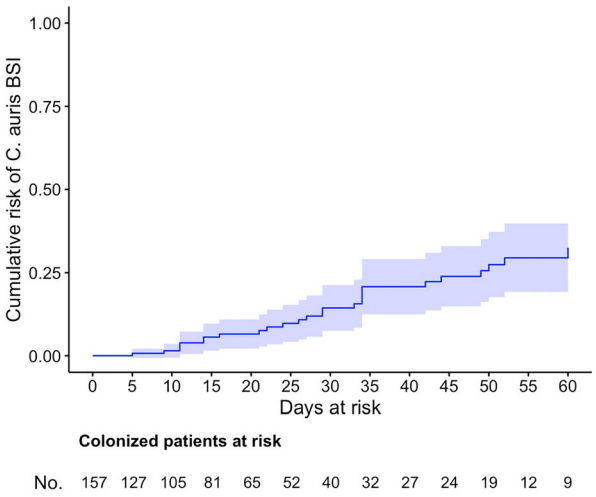

Fig. 1 Cumulative risk of *Candida auris* candidemia in colonized ICU patients. The risk was estimated by means of the Aalen–Johansen method, with the first occurring *C. auris* candidemia as the event of interest, death as a competing event, and discharge from the ICU as a right-censoring event. *BSI* bloodstream infection, *ICU* intensive care unit

detection of colonization, as shown in Fig. 1. Among patients with candidemia, 7/27 (26%) developed late recurrent *C. auris* candidemia. AFST revealed that all isolates causing the first episode of candidemia were resistant to fluconazole (MIC_{50}/MIC_{90}: > 256 mg/L) and susceptible to echinocandins (MIC_{50}: 0.12 mg/L; caspofungin/anidulafungin MIC_{90}: 0.25 mg/L, micafungin MIC_{90}: 0.12 mg/L), while 15/27 (56%) were resistant to amphotericin B (MIC_{50}/MIC_{90}: 2 mg/L). During late recurrent episodes, emergent resistance to caspofungin (MIC: 4 mg/L), despite retained susceptibility to other echinocandins, and amphotericin B (MIC: 2 mg/L) occurred in one case each (14% respectively). All patients received antifungal treatment with an echinocandin. A combination of anidulafungin and flucytosine was administered for treating the late recurrent episode caused by the isolate with caspofungin MIC 4 mg/L.

Overall, 30-day mortality after detection of *C. auris* colonization was 31% (48/157), while 30-day mortality after the onset of *C. auris* candidemia was 26% (7/27). Of note, four out of seven patients (57%) died within 30 days after the onset of late recurrent candidemia.

Table 2 shows the results of the univariable and multivariable analyses of factors potentially

Table 2 Univariable and multivariable analysis of factors associated with the development of *Candida auris* candidemia in colonized ICU patients

Variable[a]	Univariable analysis			Multivariable analysis[b]		
	Unadjusted cause-specific HR	95% CI	*P*	Adjusted cause-specific HR	95% CI	*p*
Age in years, median	1.01	0.98–1.05	0.517			
Male gender	1.76	0.70–4.41	0.230			
Charlson score, median	1.03	0.85–1.27	0.744			
Diabetes mellitus	0.92	0.35–2.46	0.875			
Chronic obstructive pulmonary disease	1.00	0.42–2.40	0.996			
Chronic kidney disease[c]	0.26	0.00–1.88	0.236			
Previous myocardial infarction	2.57	0.73–8.99	0.141			
Solid cancer	1.87	0.43–8.21	0.405			
Hematological malignancy[c]	0.80	0.09–3.09	0.800			
Solid organ transplant[c]	5.49	0.60–22.31	0.110			
Hematopoietic stem cell transplant[c]	20.83	0.14–390.53	0.163			
Admission from LTCF[c]	1.43	0.19–10.81	0.729			
Previous hospitalization	0.60	0.14–2.58	0.496			
Previous abdominal surgery	1.44	0.43–4.82	0.557			
Previous antibiotics	0.60	0.08–4.47	0.615			
Previous beta-lactams	1.16	0.16–8.66	0.886			
Previous fluoroquinolones	1.34	0.46–3.89	0.596			
Previous antifungals	1.36	0.63–2.95	0.435			
Previous azoles	1.16	0.27–4.90	0.845			
Previous polyenes	0.77	0.10–5.74	0.798			
Previous echinocandins	1.35	0.62–2.92	0.452			
Previous steroids	1.59	0.60–4.23	0.352			
Previous immunomodulatory agents	1.40	0.41–4.71	0.591			
Previous ICU stay in days	1.01	1.00–1.03	0.082	1.01	1.00–1.03	0.075
Neutropenia[c]	5.05	0.04–40.70	0.371			
COVID-19	1.50	0.63–3.59	0.361			

Table 2 continued

Variable[a]	Univariable analysis			Multivariable analysis[b]		
	Unadjusted cause-specific HR	95% CI	*P*	Adjusted cause-specific HR	95% CI	*p*
Invasive mechanical ventilation[c]	0.43	0.05–55.65	0.606			
Continuous renal replacement therapy	2.65	1.18–5.95	0.019	2.23	0.98–5.07	0.056
Extracorporeal membrane oxygenation	1.37	0.18–10.20	0.758			
Total parenteral nutrition	0.77	0.35–1.66	0.500			
Site of *C. auris* colonization						
Skin colonization[c]	2.13	0.69–10.60	0.210			
Urinary colonization	2.17	0.97–4.85	0.058			
Respiratory colonization	4.09	1.22–13.67	0.022			
Multisite colonization	9.45	1.28–70.00	0.028	9.67	1.30–71.91	0.027

COVID-19 coronavirus disease 2019, *CI* confidence intervals, *HR* hazard ratio, *ICU* intensive care unit, *IQR* interquartile range, *LTCF* long-term care facility

[a]The variables human immunodeficiency virus (HIV) infection and presence of central venous catheter (CVC) were not tested for their association with candidemia since no patients in the cohort had HIV infection and all patients in the cohort had a CVC

[b]Only results for variables included in the final multivariable model are presented

[c]Standard Cox regression model not converging. The provided results of the univariable model for this variable have been obtained by means of a penalized Cox regression with Firth correction. The model was built using the coxphf package for R Statistical Software

associated with the development of *C. auris* candidemia in colonized critically ill patients. At univariable analysis, CRRT, respiratory colonization, length of previous ICU stay, and multisite colonization showed an association with the development of *C. auris* candidemia. In the final multivariable model, only multisite colonization retained an independent association with the development of *C. auris* candidemia.

DISCUSSION

In our study, we observed a 60-day cumulative incidence of *C. auris* candidemia > 25% among colonized critically ill patients. This risk seems apparently higher than those observed in two other large European cohorts of critically ill patients. *C. auris* candidemia developed in 18% of colonized patients over 3 years at the University and Polytechnic La Fe Hospital of Valencia [16], and also in 18% of patients with *C. auris* isolation in a cardiothoracic surgery center in London over a 16-month period [17]. However, these rates were not calculated through incidence curves accounting for censoring and competing events, whereas they are similar to the crude 17% prevalence of *C. auris* candidemia in our cohort, thereby suggesting a possibly similar risk across studies.

Notably, we also found a recurrence rate of 26% after the first episode. Recurrence of *C. auris* candidemia has been to date limited to

case reports and this is the first report estimating the rate of recurrence after the first *C. auris* candidemia episode in colonized patients [18, 19].

The crude 30-day mortality rate in our study was 27%, which is coherent with the crude in-hospital mortality rate reported for *C. auris* candidemia (25–70%) [6, 20–22]. A recent meta-analysis estimated a crude mortality of 45% when restricting the analysis only to patients with candidemia, and suggested mortality to be possibly lower in the European continent [23]. We reported a far higher crude 30-day mortality in patients suffering from a second episode of *C. auris* candidemia (reaching almost 60%), although this may also reflect the severity of underlying noninfectious conditions in patients with prolonged ICU stay [9]. The high mortality we found after late recurrent episodes and its interpretation deserves further investigation in larger samples of patients with recurrent *C. auris* candidemia.

The high occurrence of antifungal resistance among clinical isolates of *C. auris* is of particular concern. In our cohort, all strains of *C. auris* causing candidemia were resistant to azoles and almost 60% were resistant to amphotericin B. None of the isolates showed baseline resistance to echinocandins, confirming that this class of antifungals frequently remains an effective option as first-line therapy for invasive *C. auris* infections. Nonetheless, our observation of a case of emergent resistance to caspofungin is alarming and should prompt further efforts not to jeopardize effective treatment options against this possibly multidrug-resistant yeast. In the latter case, however, AFST results should be carefully interpreted concerning caspofungin, since the concomitant susceptibility to other echinocandins might also suggest a paradoxically improved level of survival (a phenomenon commonly observed with echinocandins in *Candida* species) rather than emergent resistance.

All considered, there is a specific interest in preventing the occurrence of *C. auris* in colonized patients. In a cohort of 206 colonized critically ill patients, the presence of CVC and arterial catheter, total parenteral nutrition, diabetes mellitus, chronic kidney disease, CRRT, invasive mechanical ventilation, previous surgical intervention, multifocal colonization, and previous exposure to antifungals or antibiotics were independently associated with the development of *C. auris* candidemia [16]. Other published studies did not focus specifically on colonized patients and did not differentiate predictors of *C. auris* infections from those of colonization [21, 24, 25]. In our study, only multisite *C. auris* colonization (skin, respiratory, and/or urinary) retained a significant association with development of *C. auris* candidemia in colonized patients. Such a difference with previous reports might be attributed to the even distribution of some risk factors in our population (indwelling CVC, prior antibiotics exposure, mechanical ventilation). Moreover, differences in the baseline characteristics between our cohort and the Spanish one should be underlined [16]. Indeed, COVID-19 patients accounted for more than half of our colonized patients, while surgical patients were only a minority. The absence of association with "classical" risk factors of invasive candidiasis due to their wide distribution in our population (and likely in other ICU populations similar to ours) [26] should further stress the importance of preventing colonization as a crucial measure to indirectly curtail the overall impact of *C. auris* on mortality in critically ill patients.

The main limitation of our study is its retrospective design. Moreover, despite the fact that a quite large population of *C. auris*-colonized patients was included compared to current literature, power may still have remained suboptimal for some analyses (e.g., we found possible associations with the development of *C. auris* candidemia at borderline statistical significance for previous length of ICU stay and CRRT, deserving further investigation). Furthermore, the retrospective nature of the analysis precluded the collection of a sufficient amount of information to properly model potential predictors of candidemia such as days of CVC, days of antifungals, days of total parenteral nutrition, and invasive procedures as time-dependent covariates in Cox regression models. Finally, the rate of late recurrent *C. auris* candidemia might have been affected by the small denominator.

CONCLUSIONS

The cumulative incidence of *C. auris* candidemia in colonized critically ill patients may exceed 25% at 60 days. Multisite *C. auris* colonization is associated with the development of *C. auris* candidemia, suggesting that a higher fungal load may predispose to invasive infections. Our results support the importance of adequate infection control measures to prevent colonization with *C. auris,* thereby indirectly reducing the burden of morbidity and mortality associated with the development of *C. auris* candidemia.

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Compliance with Ethics Guidelines. The study was approved by the Ethics Committee of the Liguria region (N. CER Liguria 31/2022). Specific informed consent for this study was waived due to the retrospective nature of the analyses.

Data Availability. The data presented in this study are available upon scientifically sounded request from the corresponding author.

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