

The Clinical Characteristics and Risk Factors for Poor Prognosis Among HIV Patients with *Talaromyces Marneffe* Bloodstream Infection

Jianjun Sun

Shanghai Public Health Clinical Center

Weiwei Sun

Shanghai Public Health Clinical Center

Yang Tang

Shanghai Public Health Clinical Center

Renfang Zhang

Shanghai Public Health Clinical Center

Li Liu

Shanghai Public Health Clinical Center

Yinzhong Shen

Shanghai Public Health Clinical Center

Jiangrong Wang

Shanghai Public Health Clinical Center

Jun Chen

Shanghai Public Health Clinical Center

Tangkai Qi

Shanghai Public Health Clinical Center

Zhenyan Wang

Shanghai Public Health Clinical Center

Wei Song

Shanghai Public Health Clinical Center

Yixiao Lin

Shanghai Public Health Clinical Center

Shuibao Xu

Shanghai Public Health Clinical Center

Hong-zhou Lu (✉ luhongzhou@fudan.edu.cn)

Shanghai Public Health Clinical Center

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Abstract

Background *Talaromyces marneffei*(TM) bloodstream infection is common in AIDS patients with extreme immunodeficiency in Southeast Asia and South China, however, clinical case study on TM bloodstream infection is scarce. We retrospectively analyze the clinical characteristics of TM bloodstream infection in hospitalized AIDS patients and determine the outcomes of hospitalization after diagnosis in our hospital over the past 5 years.

Methods From January 2015 to July 2020, cases of TM detected by blood culture in patients admitted to our center were sorted and analyzed. The admission complaints, blood cells, biochemistry, CD4/CD8 count and 1,3- β -D-glucan, procalcitonin, CRP level on the day of blood culture test, and outcomes during hospitalization were analyzed. Logistic regression analysis was performed for the risk factors for poor prognosis. Spearman correlation analysis was used to analyze the correlation between peripheral blood cells, albumin and the time required for TM to become positive in blood culture. The difference was statistically significant when the P value was <0.05.

Results A total of 87 patients were collected, with a median age of 34 years, a median hemoglobin of 94 g/L and CD4 count of 7/ μ l. The rate of TM bloodstream infection among all in-hospital patients increased from 0.99% in 2015 to 2.09% in 2020(half year). Patients with TM bloodstream infection with a CD8 count <200/ μ l had a 12.6-fold higher risk of poor prognosis than those with a CD8 count >200/ μ l (p=0.04), and those with 1,3- β -D-glucan <100 pg/mL had a 34.9-fold higher risk of poor prognosis than those with 1,3-beta-D-glucan >100 pg/mL (p=0.01).

Conclusions TM bloodstream infection is becoming more common in advanced AIDS patients in endemic areas. For those patients with extremely low CD4 and CD8 cell counts below 200/ μ l, the 1,3- β -D-glucan <100 pg/mL are with an increased risk of poor prognosis.

Background

AIDS patients are susceptible to multiple opportunistic infections at the late stage, especially when the CD4 count is below 50/ μ l[1, 2]. The spectrum of bloodstream infection varies among people living with AIDS in different geographical settings[3]. *Talaromyces marneffei* (formerly *Penicilliosis marneffei*) is endemic in Southeast Asia[4], Northeastern India[5], and Southern China[6]. The first natural human case of *Talaromycosis* (*Penicillo*sis) was reported in 1973 and involved an American minister with Hodgkin's disease who lived in Southeast Asia[7]. TM was first reported in mainland China by Z.L. Deng in 1984[8] and in Vietnam by T.V. Hien in 2001[9]. Recently, TM has become an emerging pathogen in immunocompromised patients in mainland China[7]; furthermore, the number of confirmed cases of TM is increasing quickly in mainland China[10]. The incidence rates of TM infection range from 4–14%, with an associated mortality of 10–30%[11]. Reports of TM disease are common in the AIDS population in the late stage. A meta-analysis [12] showed that the prevalence of TM among HIV patients in China ranged from 0.2% (95% CI: 0.1–0.5%) to 26.5% (95% CI: 16.2–43.5%). South China had the highest prevalence,

estimated at 15.0% (95% CI: 11.0-20.4%), while Southwest China had the lowest prevalence, estimated at 0.3%[13]. It is estimated that there will be 4,951 TM cases per year in patients with AIDS in southern China by 2050, and the endemic areas are increasing[12]. The disease is mostly confirmed in the lungs and skin and is related to TM contact by inhalation or direct contact[14, 15]. However, in clinical settings, because the onset of the disease is relatively insidious and mild, the clinical symptoms are not very typical, and patients often experience delayed diagnosis or misdiagnosis by doctors who are not familiar with the symptoms of TM disease. Although they are finally diagnosed with TM, there are multiple organ lesions, such as superficial lymphadenopathy, abdominal pain, hepatosplenomegaly, mediastinal lymph node enlargement, bone marrow involvement and hematopenia[16]. TM bloodstream infection is a kind of TM disease, especially in AIDS patients with extreme immunodeficiency; however, clinical case studies on TM bloodstream infection are scarce. Our hospital is a referral center for AIDS patients in East China and many AIDS patients were admitted in hospital every year. The aim of this study was to retrospectively analyze the clinical characteristics of TM bloodstream infection in hospitalized AIDS patients and determine the outcomes of hospitalization after diagnosis in our hospital over the past 5 years.

Methods

The design and setting of the study

Retrospectively collected from January 1st 2015 to July 31th 2020, cases of TM detected by blood culture in patients admitted to the Shanghai Public Health Clinical Center (SPHCC) were sorted and analyzed. Electronic medical records of HIV-infected patients diagnosed with TM bloodstream infection (defined by a culture positive for TM from patient blood) were searched. Information including place of birth or long-term residence, presenting complaints and physical examinations (fever, umbilical fovea-like rash[17], and superficial lymphadenopathy), and laboratory tests (routine blood test, biochemistry, procalcitonin, CD4/CD8 T-cell count, CRP and outcomes during hospitalization) were analyzed. Blood culture tests were performed on patients with fever, loss of weight, lymphadenopathy or other symptoms need considering infection on the time of getting admission, and routine blood tests and tests for biochemistry, cellular immune function, procalcitonin and CRP were measured at the same time as blood culture. The patients were divided into a survival group and a poor prognosis group (death or having given up treatment due to advanced severe disease and being discharged from the hospital before death) according to their final clinical outcomes during the hospital admission.

SPHCC is the designated hospital for HIV patients in Shanghai municipality and is also a tertiary referral hospital for refractory and complicated HIV-infected cases in China. Cultures of clinical specimens were established on Sabouraud's dextrose agar at 25 °C and 37 °C[18].

The characteristics of participants

Among 8621 cases (from January 1st 2015 to July 31th 2020) admitted to SPHCC, there were 662 positive blood culture results and including 87 cases with TM bloodstream infection.

Statistical methods

The rank sum test was used for the comparison of demographics and clinical characteristic data between the two groups; chi-square analysis was used for the comparison of categorical variables. The predictors included in the multivariate model were selected based on a significance level of $p < 0.1$ in the univariate analyses. The confounding factors retained in the multivariate model were serum procalcitonin (> 0.60 ng/mL), CD8 count level ($< 200/\mu\text{l}$), 1,3-beta-D-glucan (< 100 pg/mL) and blood urea nitrogen level (> 4 mmol/L). Spearman correlation analysis was used to analyze the correlation between peripheral blood cells, albumin and the time required for TM to become positive in blood culture. The difference was statistically significant when the P value was < 0.05 . Data analysis was conducted using IBM SPSS version 20.0 (IBM SPSS, Inc., Armonk, NY, USA).

Results

Case distribution and trends in TM bloodstream infection

Among 8621 cases (from January 1st 2015 to July 31st 2020) admitted to SPHCC, the rate of TM bloodstream infection among all in-hospital patients was 13 (0.99%) in 2015, and in 2019, it grew to 18 (1.01%). Since July 2020, the rate was 2.09%. Because SPHCC is a referral hospital in China, all TM bloodstream infection cases were scattered throughout many provinces, Zhejiang (24 cases) and Jiangxi (13 cases) were the two provinces with the largest number of TM bloodstream infection cases in this analysis.

The comparison of clinical and laboratory features between the two groups with different clinical outcomes

The median age of patients with TM bloodstream infection was 34 years, the median hemoglobin level was 94 g/L, and the median CD4 count was $7/\mu\text{l}$. The median time required for TM culture conversion (from taking blood culture to TM identified) was 8 days. The blood urea nitrogen level, procalcitonin and CRP in the poor prognosis group were significantly higher than those in the survival group; the peripheral blood CD8 count, 1,3- β -D-glucan, and serum albumin in the poor prognosis group were significantly lower than those in the survival group; the count levels of hemoglobin and CD4 in the poor prognosis group were lower than those in the survival group, but the difference was not significantly different. There was no significant difference in age or gender rate between the two groups. Among the 87 cases with TM bloodstream infection, there were 10 cases of NTM disease (6 cases of pulmonary NTM disease, 3 cases of NTM blood infection, 1 case of intestinal NTM disease); 10 cases of PCP; 9 cases of oral candidiasis; 8 cases of CMVR; 5 cases of combined tuberculosis infection, including 3 cases of tuberculosis, 1 case of lymphotuberculosis, 1 case of tuberculous pleurisy; and 1 case of cryptococcal meningitis. For patients with poor prognosis, the median length of hospital stay was 5 days, with a minimum of 1 day and a maximum of 22 days; for patients with normal discharge, the median length of hospital stay was 22 days (See Table 1).

Table 1
The demographics and clinical characteristic of TM bloodstream infection patients

Demographics and clinical data	Normal range	Total cases (n = 87)	Survival cases (n = 72)	Poor prognosis (n = 15)	P value
Age (years)	–	34.0(28.0–44.0)	33.5(27.3–43.0)	37.0(30.0–46.0)	0.71
Male (%)	–	81(93%)	68(94%)	13(87%)	0.28*
WBC (*10 ⁹ /L)	3.5–9.5	3.4(2.4–5.1)	3.4(2.4–4.9)	4.5(2.1–8.1)	0.57
Neutrophil (*10 ⁹ /L)	1.8–6.3	2.9(1.7–4.2)	2.9(1.7–4.0)	2.4(1.6–6.5)	0.65
Hemoglobin (g/L)	115–150	94(81–107)	95(81–107)	86(80–104)	0.30
Platelet (*10 ⁹ /L)	125–350	100(66–155)	99.5(72.3–149.3)	103(23–198)	0.60
CD4 count (/ul)	410–1590	7(4–19) N [†] =84	9(4–21) N [†] =71	5(3–12) N [†] =13	0.05
CD8 count (/ul)	190–1140	202(98–336) N = 82	223(106–384) N = 70	122(57–186) N = 12	0.01
Ratio of CD4/CD8	0.9–3.6	0.04(0.02–0.10) N = 82	0.04(0.02–0.10) N = 70	0.06(0.03–0.10) N = 12	0.74
BUN (mmol/L)	2.6–7.5	4.1(3.2–6.0) N = 86	4.0(3.1–5.4) N = 72	6.6(4.0–12.2) N = 14	0.001
Serum Albumin (g/L)	40–55	27(23–31) N = 86	28(24–31) N = 72	25(22–28) N = 14	0.07
PCT (ng/mL)	0–0.05	0.63(0.21–1.75) N = 74	0.50(0.19–1.65) N = 63	1.09(0.62–15.45) N = 11	0.04
CRP (mg/L)	0–10	54(26–88) N = 76	44(24–81) N = 63	71(53–111) N = 13	0.03
BDG (pg/mL)	< 60	194(48–264) N = 74	205(101–287) N = 62	54(10–222) N = 12	0.01

* By Fihser exact test; Others by Manny-Whitney test; †N, means some of the cases with the clinical data and being collected in this analysis. WBC: White blood cell; BUN: Blood urea nitrogen; PCT: Procalcitonin; CRP: C-reactive protein; BDG: 1,3-β-D-Glucose; TB: Tuberculosis; NTM: Nontuberculous mycobacteria; CMVR: Cytomegalovirus rentinitis; PCP: Pneumocystis carinii pueumonia; PCP: Pneumocystis jirovecii pueumonia.

Demographics and clinical data	Normal range	Total cases (n = 87)	Survival cases (n = 72)	Poor prognosis (n = 15)	P value
Fever	–	81(93.1%)	67(93.1%)	14(93.3%)	0.97*
Rash	–	31(35.6%)	26(36.1%)	5(33.3%)	0.84*
Lymphnode enlargement	–	25(28.7%)	21(29.2%)	4(26.7%)	0.85*
TB coinfection	–	5(5.7%)	5(6.9%)	0(0%)	0.29*
NTM disease	–	10(11.5%)	9(12.5%)	1(6.7%)	0.52*
CMVR	–	8(9.2%)	8(11.1%)	0(0%)	0.18*
PCP	–	10(11.5%)	8(11.1%)	2(13.3%)	0.81*
Cryptococcal meningitis	–	1(1.1%)	1(1.4%)	0(0%)	0.65*
Oral candiditis	–	9(10.3%)	5(6.9%)	4(26.7%)	0.02*
Hospital stay (days)	–	21(16–25)	22(19–26)	5(3–13)	< 0.0001
Culture conversion days	–	8(6–9)	8(6–9)	6(5–9)	0.12
<p>* By Fihser exact test; Others by Manny-Whitney test; †N, means some of the cases with the clinical data and being collected in this analysis. WBC: White blood cell; BUN: Blood urea nitrogen; PCT: Procalcitonin; CRP: C-reactive protein; BDG: 1,3-β-D-Glucose; TB: Tuberculosis; NTM: Nontuberculous mycobacteria; CMVR: Cytomegalovirus rentinitis; PCP: Pneumocystis carinii pueumonia; PCP: Pneumocystis jirovecii pueumonia.</p>					

Risk factors for TM bloodstream infection patients with poor prognosis

Of the 87 cases in the study, 27 cases with incomplete data (CD4, CD8 count, PCT, albumin) were excluded, and 60 cases remained (11 with poor prognosis and 49 survival cases). The age, peripheral blood cells, serum albumin, CD4 count level, CD8 count level, and the time required for blood culture conversion, and the procalcitonin, 1,3-beta-D-glucan, and blood urea nitrogen levels of the patients were analyzed by logistic test for risk factors for poor prognosis. Univariate analysis showed that serum procalcitonin (> 0.60 ng/mL), CD8 count level (< 200/μl), 1,3-beta-D-glucan (< 100 pg/mL) and blood urea nitrogen level (> 4 mmol/L) were risk factors for poor prognosis. The above four factors were included in the multivariate analysis, and the results showed that the risk of poor prognosis was 12.6 times higher in patients with CD8 count < 200/μl than in those with CD8 count > 200/μl (p = 0.04) and 34.9 times higher in those with 1,3-beta-D-glucan < 100 pg/mL than in those with 1,3-beta-D-glucan > 100 pg/mL (p = 0.01) (See Table 2).

Table 2

Logistic regression analysis of the risk factors for poor prognosis of patients with TM bloodstream infection

Variable	Crude odds ratio (COR)	95% confidence interval (CI)	Adjusted odds ratio (AOR)	95% confidence interval (CI)	P-value
Years	Reference	--			
≥ 35 years old	1.15	0.31–4.28			
WBC	Reference	--			
≥ 3.5*10 ⁹ /L	0.8	0.22–2.97			
N	Reference	--			
≥ 2*10 ⁹ /L	1.29	0.30–5.54			
Hb	Reference	--			
≥ 90 g/L	0.44	0.12–1.67			
PLT	Reference	--			
≥ 100*10 ⁹ /L	0.98	0.26–3.64			
Albumin	Reference	--			
≥ 26 g/L	0.28	0.07–1.09			
CD4	Reference	--			
≥ 5/ul	0.44	0.12–1.67			
CRP	Reference	--			
≥ 65 mg/L	3.01	0.77–11.73			
Culture conversion days	Reference	--			
≥ 6 days	0.24	0.04–1.27			
PCT	Reference	--	Reference	--	--
≥ 0.60 ng/mL	5.09	1.00–26.00	8.47	0.55–129.41	0.13
CD8	Reference	--	Reference	--	--
< 200/ul	6.53	1.27–33.46	12.64	1.08–148.54	0.04
1,3-β-D-Glucose	Reference	--	Reference	--	--

WBC: white blood cell; N: neutrophil; Hb: hemoglobin; PLT: Platelet; PCT, Procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen

Variable	Crude odds ratio (COR)	95% confidence interval (CI)	Adjusted odds ratio (AOR)	95% confidence interval (CI)	P-value
< 100 pg/mL	4.68	1.18–18.51	34.85	2.34–519.10	0.01
BUN	Reference	–	Reference	–	–
≥ 4 mmol/L	5.52	1.08–28.25	2.4	0.30–19.00	0.41

WBC: white blood cell; N: neutrophil; Hb: hemoglobin; PLT: Platelet; PCT, Procalcitonin; CRP: C-reactive protein; BUN: blood urea nitrogen

The correlation between laboratory tests and the time to TM positive conversion in blood culture

Spearman correlation analysis was performed with the time to TM positive conversion in blood culture as the dependent variable and the levels of peripheral leukocytes, neutrophils, hemoglobin, platelets, albumin and PCT, and 1,3-β-D-glucan as independent variables. The results showed that the levels of both platelets ($r = 0.37$, $p = 0.0004$) and albumin ($r = 0.44$, $p < 0.0001$) were positively correlated with the time required for TM blood culture conversion, and the levels of PCT ($r = -0.40$, $p = 0.0009$) and 1,3-β-D-glucan ($r = -0.30$, $p = 0.0076$) were negatively correlated with the time required for TM positive in blood culture.

Discussion

The number of TM bloodstream infection cases among in-hospital patients increased from 2015 (13 cases) to 2019 (18 cases) at SPHCC. The rate of TM bloodstream infection among admitted patients increased from 0.99% in 2015 to 2.09% in 2020 (from January to July). According to a systematic review by Qin et al.[13], the estimated pooled prevalence of TM infection in China was 3.3% (95% CI: 1.8–5.8%), and the prevalence in Shanghai was 1.8% (95% CI: 1.3–2.4%), which are in line with our findings. As a referral center, we treat many kinds of opportunistic infections, including TM, and based on the etiology study of bloodstream infection among in-hospital patients in 2016[3], TM bloodstream infection accounted for 18.8% (43/299), which was the second most common bloodstream infection pathogen. With the progress of AIDS treatment and physician awareness of TM, reports of AIDS with TM infection have become increasingly common, and the prognosis depends on a timely diagnosis[19] and proper antifungal treatment[20, 21]. Immunodeficient patients from endemic areas should visit hospitals, and physicians should remain vigilant about TM symptoms and perform a specimen culture as early as possible and then initiate the antifungal regimen with Amphotericin B, Itraconazole or Voriconazole[21]. In this study, the mortality rate of patients with TM bloodstream infection was 17.2% (15/87), which is similar to 17.5% (191/1093) published by Jiang et al in 2019[6] and 16.7%[18] in our hospital from 2014 to 2015. In view of the fact that this is a single-center study from a tertiary hospital[22] where patients from all parts of the country obtain further diagnosis and treatment, it cannot represent all the patients with TM disease.

In this study, the admission blood urea nitrogen level, procalcitonin, and CRP in the poor prognosis group were significantly higher than those in the survival group; the peripheral blood CD8 count level and 1,3-β-

D-glucan level in the poor prognosis group were significantly lower than those in the survival group; in the overall presentation of patients with TM bloodstream infection, although they have extreme immunodeficiency, poor prognosis patients are often in an extremely severe inflammatory state and have poor nutritional status compared with the survival patients. As a result, the patient's condition still deteriorated with symptomatic support treatment, and eventually, the condition worsened or the patient even died within a few days after admission. Among the 15 cases of worsening illness or death in this study, the median length of hospital stay was only 5 days, which means that at the time of worsening illness or death, TM disease often had not been confirmed, which also indicates that the immunodeficiency caused by HIV infection requires early diagnosis and early intervention to avoid the development of severe immunodeficiency[23].

The presence of TM bloodstream infection is a predictor of severe immunodeficiency[4, 24]. When they are in such an immunodeficient state, patients often have coinfection, such as cytomegalovirus retinitis, pulmonary TB, NTM disease, and cryptococcal meningitis.[22, 25]. There were fewer cases of coinfection in the group with poor prognosis. Considering that the group with poor prognosis had shorter overall hospitalization time and worsened or even died soon after admission, resulting in insufficient time for diagnosis, there may be missed diagnoses and fewer confirmed diseases than those in the group of surviving patients. Patients with poor prognosis are mostly in the late stage of the disease. Although they are given symptomatic supportive treatment after hospitalization, their condition fails to improve, and they lose the chance for antifungal treatment (or other comorbidities fail to control, and their condition is incurable). Therefore, the number of hospitalization days for patients with poor prognosis was significantly less than that of normal discharged patients.

In this study, risk factor analysis of patients with poor prognosis after clinical treatment for TM bloodstream infection showed that patients with CD8 count $< 200/\mu\text{l}$ and whole blood 1,3-beta-D-glucan $< 100 \text{ pg/mL}$ had 12.6 times and 34.9 times the risk of poor prognosis, respectively. The median CD4 count was only $7/\mu\text{l}$, which belongs to the extremely immunodeficient population; the CD8 cell count was still significantly reduced, and the median count was only $202/\mu\text{l}$. CD8 counts may predict prognosis independently of CD4 counts[26]. In most cases, HIV infection severely progresses, CD4 and CD8 are depleted[27]. This may explain why a delay in the diagnosis of TM independently predicted the early mortality of the patients[28, 29].

For the 1,3- β -D-glucan (BDG) level, this study found that those with a BDG less than 100 pg/mL are at risk for poor prognosis. This unexpected finding may be explained by the fact that late diagnosis is the main reason for the high mortality in TM-infected patients[30]. As mentioned previously, the BDG assay is helpful in the early detection of invasive fungal disease[31], including TM[32, 33]. The possible reason for this finding is that in clinical practice, using this marker as important evidence for fungal infection may cause delays in empirical diagnosis and treatment of patients with fever but low BDG levels; after all, blood culture results take time. Antifungal treatment may be initiated earlier in patients with high levels of BDG than in patients with low levels of BDG. Furthermore, in our analysis, when using the Spearman correlation, BDG was negatively correlated with the time required for blood culture to detect TM.

There are some limitations of this study. First, because this is a retrospective analysis, the clinical data, such as treatment regimen administered before admission in our hospital, records of patients' visit experience, as well as the time from onset of symptoms to diagnosis, all affect the accuracy of descriptions and analysis. Second, this was a single-center study, and caution should be paid to making a summary or comparison with the population in areas with a high incidence of TM disease in China.

Conclusions

Bloodstream infections caused by TM are becoming increasingly common in the AIDS population with severe immunodeficiency in East China. For those with extremely low CD4 and CD8 cell counts below 200/ul, the 1,3- β -D-glucan < 100 pg/mL are with an increased risk of poor prognosis. Improving the awareness of symptoms such as umbilical fovea rash, fever and lymphadenopathy has a positive effect on early diagnosis of the disease and optimization of treatment efficacy.

Abbreviations

TM: *Talaromyces marneffeii*; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; WBC: White blood cell; BUN: Blood urea nitrogen; PCT: Procalcitonin; CRP: C-reactive protein; BDG: 1,3- β -D-Glucose; TB: Tuberculosis; NTM: Nontuberculous mycobacteria; CMVR: Cytomegalovirus retinitis; PCP: *Pneumocystis jirovecii* pneumonia.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Shanghai Public Health Clinical Center (Ethics approval No. 2017-S022-04). This study used retrospective and anonymous data collection methods, which did not involve patient privacy, so informed consent was exempted from ethical review.

Consent for publication Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files(S1 File).

Competing interests The authors declare that they have no competing interests.

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Authors' contributors HZL, JJS and WWS conceived and designed the study; JJS and WWS, YT, RFZ,LL,YZS, JRW,JC,ZYW,WS,TKQ and SBX, YXL collected the data. JJS, WWS and YT, RFZ,LL,YZS, JRW,JC analyzed the data; JJS, WWS and HZL interpreted the results; JJS wrote the first draft; JJS, WWS, HZL, RFZ, LL,YZS, JRW, JC, ZYW,WS,TKQ, YT,SBX and YXL contributed to the final version. All authors have read and approved the manuscript.

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