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ORIGINAL RESEARCH

Evaluation of Different Blood Culture Bottles for the Diagnosis of Bloodstream Infections in Patients with HIV

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ABSTRACT

Introduction: Bloodstream infection (BSI) is a significant factor contributing to hospitalization and high mortality rates among human immunodeficiency virus(HIV)-positive patients. Therefore, the timely detection of this condition is of utmost importance. Blood culture is considered the gold standard for diagnosing BSIs. Currently, BD BACTEC™ Plus Aerobic/F culture bottles and the BD BACTEC™ Myco/F Lytic culture bottles can be used for blood culture. This study aimed to evaluate the efficacy of two different types of culture bottles in diagnosing BSIs in patients with HIV.

Methods: A retrospective analysis was conducted on HIV-positive patients hospitalized in the Infection Department of Wenzhou Central Hospital between July 2019 and October 2021. A total of 246 pairs of blood samples were included, consisting of an aerobic culture vial and a Myco/F culture vial. Blood culture results and clinical diagnosis were utilized to identify the presence of BSI.

Results: Out of 246 cases, 84 cases had positive blood cultures. Fungal BSIs, particularly *Talaromyces marneffei* BSIs, were the most prevalent among patients with HIV. The positive rate of Myco/F culture bottles (89.29%) was significantly higher compared with aerobic culture bottles (69.05%; $P = 0.001$). In the diagnosis of fungal BSIs, the positive rate of Myco/F culture bottles was 88.57%, which was significantly higher than that of aerobic culture bottles (72.86%; $P = 0.018$). The Myco/F culture bottle has more advantages in diagnosing *Talaromyces marneffei* BSIs (P=0.028). In addition, mycobacteria were exclusively detected in Myco/F culture bottles.

Conclusions: Fungal BSIs are the predominant type of infections in HIV-positive patients. Myco/F culture bottles exhibit noteworthy attributes of high positive rate in diagnosing HIV combined with BSI. These advantages are conducive to obtaining accurate culture results and minimizing missed diagnoses.

Keywords: Bloodstream infection; Blood culture; HIV/AIDS; Diagnosis; Fungi

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Key Summary Points

Why carry out this study?

The mortality rate of bloodstream infection (BSI) in HIV-positive patients is high, and understanding the type of BSI is crucial.

The aerobic/F culture bottles and the Myco/F Lytic culture bottles are available for diagnosing BSI. However, evaluation of different blood culture bottles for the diagnosis of BSI in patients with HIV has rarely been reported.

What was learned from the study?

Fungal BSI is the predominant type of infections in HIV-positive patients in eastern China.

The Myco/F culture bottles exhibit more advantages than traditional culture bottles in diagnosing HIV combined with BSI.

INTRODUCTION

Previous studies conducted in various regions of the world have consistently demonstrated that bloodstream infections (BSIs) are prevalent among individuals living with human immunodeficiency virus(HIV)/acquired immunodeficiency syndrome (AIDS), highlighting their role as a major contributor to mortality within this population [1–3]. Compared with HIV-seronegative patients, HIV-infected individuals exhibited a significantly higher mortality rate due to BSI, with 30-day mortality reaching up to 28% [1]. The mortality rate of BSIs is influenced by both the specific pathogen involved and the timely diagnosis. According to a study, the mortality rate varied from 10% in patients with HIV with *Mycobacterium tuberculosis* BSI who did not receive timely anti-tuberculosis treatment to 27% in those who experienced treatment delays [4]. The etiological spectrum of BSIs also varies across different regions. Notably, Enterobacteriaceae, particularly *Escherichia coli*, emerged as the most prevalent organisms involved in BSIs among patients with HIV in Italy [2, 5]. In China, the majority of BSIs are caused by mycobacteria and fungi [6]. Thus, gaining knowledge about the range of pathogens causing BSIs in patients with HIV in the region becomes crucial to promptly initiate empirical treatment prior to the availability of blood culture results.

Despite recent advancements in microbiological biomolecular techniques, blood culture continues to be the most practical and reliable method for diagnosing BSIs. Various types of bottles are available for blood cultures, including traditional culture vials such as BD BACTEC™ Plus Aerobic/F and BD BACTEC™ Plus Anaerobic/F bottles, as well as BD BACTEC™ Myco/F Lytic (Myco/F) bottles. Aerobic and anaerobic culture vials are designed to detect both bacteria and fungi. However, any negative bottles are discarded after 5 days of incubation. In contrast, Myco/F bottles are capable of detecting not only bacteria and fungi but also mycobacteria. The blood culture is incubated for a maximum period of 42 days. Several studies have demonstrated that Myco/F culture bottles exhibit a higher positivity rate than aerobic bottles in candidemia populations [7, 8]. However, none of these studies have focused on other fungi, such as *Talaromyces marneffei*. Furthermore, there is a scarcity of studies comparing traditional blood culture vials and Myco/F culture bottles in patients with HIV with BSIs. Therefore, it is intriguing to determine the superiority of Myco/F culture bottles or traditional culture bottles in detecting pathogens in patients with HIV with BSI.

In this study, we tried to elucidate the clinical features and etiology of BSI in patients with HIV and compare the effectiveness of traditional culture bottles and Myco/F culture bottles in directly identifying pathogens from positive blood cultures.

METHODS

Study Population

This retrospective study focused on HIV-infected inpatients (age ≥ 18 years) who were admitted to the Department of Infectious Diseases at Wenzhou Central Hospital between July 2019 and October 2021. Blood samples were collected within 48 h of hospitalization. Patients who did not undergo blood cultures or who used only one type of bottle (either traditional culture bottle or Myco/F culture bottle) were excluded. Patients with incomplete information were excluded. Blood samples from each patient were collected from the same site and at the same time, with one sample placed in the Myco/F culture bottle and the other in the traditional culture bottle. Subsequently, both samples were processed concurrently in the laboratory. This study was approved by the ethics review boards of Wenzhou Central Hospital (approval no. L2022-01-033). Informed consent from patients was waived due to the retrospective nature of this study.

Laboratory Methods

The low positive rate of anaerobic culture bottles and the presence of the same pathogenic bacteria in aerobic culture bottles excluded them from the analysis in this study. The blood sample was collected for culture, with 10 mL allocated for aerobic culture bottles (BD, New Jersey) and 10 mL for Myco/F Lytic culture bottles (BD, New Jersey). The blood culture bottles were incubated using the BD BACTEC™ FX automated blood culture system (BD, New Jersey). As per the laboratory protocol, aerobic culture bottles were placed in the blood culture system for a maximum of 5 days, whereas Myco/F culture bottles were 42 days. The automated blood culture system was prompted when microbial growth was detected in a culture bottle. Positive cultures were then transferred to the culture medium, and a Gram stain was performed to identify whether the bacteria was Gram-positive or Gram-negative. A Bruker mass spectrometer (Accexp Co., Ltd., Changsha, China) was utilized for the identification of bacterial and fungal species. An acid-fast stain was used to identify whether the specimen was mycobacteria. The definition of contamination is that skin flora was detected from only one culture bottle, and was judged by two experienced infectious diseases specialists.

If mycobacteria were suspected, an acid-fast stain was used to determine if it was acid-fast bacteria. Subsequently, the *Mycobacterium tuberculosis* antigen kit (Genesis Biodetection Biocontrol Ltd., Hangzhou, China) was employed to differentiate between *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM) when the acid-fast stain yielded a positive result. Finally, a chip was utilized for species identification when the strains were classified as NTM.

Statistical Analysis

Proportions and medians were utilized to describe patient demographics and clinical characteristics. Pearson's chi-square test or Fisher's exact test was performed to assess the differences between the two groups. *P*-values less than 0.05 were deemed statistically significant. Data analyses were performed using SPSS 22.0 software (SPSS Co. Ltd., Chicago, IL, USA).

RESULTS

Clinical Characteristics and Isolates of Study Participants

Our final analysis included a total of 246 patients with HIV who were admitted to Wenzhou Central Hospital between July 2019 and October 2021. Among these patients, 84 (34.15%) had BSIs, all of whom were community-acquired. The remaining 162 patients (65.85%, including those with contaminated blood cultures) did not have a BSI. According to Table 1, the HIV-infected population with BSI had a younger age distribution (median age of 38.5 years versus 47 years; $P = 0.001$) compared with those without BSI. In comparison to non-BSI patients, BSI patients exhibited a

Table 1 Clinical characteristics in patients with HIV

Characteristics, number (%)	Total (n = 246)	BSI (n = 84)	Non-BSI (n = 162)	P-value	χ^2 value
Male sex	205 (83.33%)	69 (82.14%)	136 (83.95%)	0.718	0.130
Age, median (IQR), year		38.5 (31–49)	47 (34–60.25)	0.001	
Newly diagnosed HIV	140 (56.91%)	50 (59.52%)	90 (55.56%)	0.551	0.355
Latest $CD4^+$ T cell count < 200 cells/μL	208 (84.55%)	82 (97.62%)	126 (77.78%)	< 0.001	16.673
On cART	66 (26.83%)	12 (14.29%)	54 (33.33%)	0.001	10.223
Type of isolate[a]					
Bacteria	8 (3.52%)	8 (9.52%)	–	–	
Mycobacteria	7 (2.85%)	7 (8.33%)	–	–	
Fungi	70 (28.46%)	70 (83.33%)	–	–	
Diagnoses					
Talaromycosis	68 (27.64%)	63 (75%)	5 (3.09%)	< 0.001	146.841
PJP	60 (24.39%)	18 (21.43%)	42 (25.93%)	0.436	0.607
Cryptococcosis	22 (8.94%)	11 (13.10%)	11 (6.79%)	0.100	2.701
Tuberculosis	30 (12.20%)	6 (7.14%)	24 (14.81%)	0.081	3.041
CMV infection	52 (21.14%)	20 (23.81%)	32 (19.75%)	0.460	0.546
Candidiasis	70 (28.46%)	36 (42.86%)	34 (20.99%)	< 0.001	12.996

Abbreviations: *BSI* bloodstream infection, *IQR* interquartile range, *cART* combination antiretroviral therapy, *PJP Pneumocystis jirovecii* pneumonia, *CMV* cytomegalovirus
[a]Excluding contaminants

significantly higher proportion of individuals with a latest $CD4^+$ T cell count below 200 cells/mL (97.62% versus 77.78%). Furthermore, BSI patients had higher prevalence rates of talaromycosis (75% versus 3.09%; $P < 0.001$) and candidiasis (42.86% versus 20.99%; $P < 0.001$) than that of non-BSI patients. The proportion of patients who had a BSI and initiated combination antiretroviral therapy (cART) before this onset was lower compared with those who did not have a BSI (14.29% versus 33.33%; $P = 0.001$). Among the patients with BSIs, 8 had bacterial infections, 6 had mycobacterial infections, and 69 had fungal infections. One patient had coinfection with both fungus and mycobacteria.

Etiology of BSI in Patients with HIV

A total of 142 positive blood cultures were recorded in both the Myco/F culture bottles and aerobic culture bottles (Table 2). Among these, 113 (79.58%) were identified as fungal infections, comprising 100 (70.42%) *T. marneffei* infections, 12 (8.45%) *Cryptococcus neoformans* infections, and 1 (0.70%) *Candida albicans* infection. Out of the total infections, seven were caused by mycobacteria, with five cases (3.52%) related to *Mycobacterium tuberculosis* (MTB) and two cases (1.41%) related to nontuberculosis mycobacteria (NTM). A total of 13 cases were other bacterial infections, such as *Staphylococcus hominis* (n = 5), *Salmonella enterica* (n = 5), and *Klebsiella pneumoniae* (n = 3). Moreover, eight patients were contaminated

Table 2 Distribution of microorganisms isolated in bloodstream infection among HIV-infected patients

Microbiological isolates	Number (%) of isolates from aerobic bottles	Number (%) of isolates from Myco/F bottles	Total number (%) of isolates
Fungi	51 (82.26%)	62 (78.48%)	113 (79.58%)
T. marneffei	45 (72.58%)	55 (69.62%)	100 (70.42%)
Cryptococcus neoformans	6 (9.68%)	6 (7.59%)	12 (8.45%)
Candida albicans	ND	1 (1.27%)	1 (0.70%)
Mycobacterium	ND	7 (8.86%)	7 (4.93%)
Mycobacterium tuberculosis	ND	5 (6.33%)	5 (3.52%)
NTM[a]	ND	2 (2.53%)	2 (1.41%)
Other bacteria (excluding contaminants)	7 (11.29%)	6 (7.59%)	13 (9.15%)
Staphylococcus hominis	3 (4.84%)	2 (2.53%)	5 (3.52%)
Salmonella enterica	3 (4.84%)	2 (2.53%)	5 (3.52%)
Klebsiella pneumoniae	1 (1.61%)	2 (2.53%)	3 (2.11%)
Contaminant	4[b] (6.45%)	4[c] (5.06%)	8 (5.63%)
Total	62	79	142

Abbreviation: *ND* not detected, *NTM* nontuberculosis mycobacteria
[a]NTM data include the following species: *Mycobacterium avium*, *Mycobacterium brisbanense*
[b]Including *Staphylococcus cephalosus* (3 cultures), *Staphylococcus haemolyticus* (1 culture)
[c]Including *Staphylococcus hominis* (2 cultures), *Staphylococcus haemolyticus* (1 culture), *Corynebacterium tuberculostearicum* (1 culture)

with various bacteria, namely *Staphylococcus hominis* (n = 2), *Staphylococcus cephalosus* (n = 3), *Staphylococcus haemolyticus* (n = 2), and *Corynebacterium tuberculostearicum* (n = 1).

Aerobic Culture Bottles

Of the total cases, 51 were identified as fungal infections, with 45 cases attributed to *T. marneffei* and 6 cases to *Cryptococcus neoformans*. No mycobacterial infections were detected in the aerobic culture bottles. Seven cases involved other bacterial infections, specifically *Staphylococcus hominis* (n = 3), *Salmonella enterica* (n = 3), and *Klebsiella pneumoniae* (n = 1). Furthermore, we observed contamination in four culture bottles, specifically *Staphylococcus cephalosus* (n = 3) and *Staphylococcus haemolyticus* (n = 1; Table 2).

Myco/F Culture Bottles

Of the total, there were 62 fungal infections, comprising 55 cases of *T. marneffei* infections, 6 cases of *Cryptococcus neoformans* infections, and 1 case of *Candida albicans* infections. Among the cases, seven were attributed to mycobacterial infections, consisting of five MTB infections and two NTM infections. Besides, six were other bacterial infections, including two cases of *Staphylococcus hominis*, two cases of *Salmonella enterica*, and two cases of *Klebsiella pneumoniae*. Furthermore, four culture bottles were found to be contaminated, with *Staphylococcus hominis* (n = 2), *Staphylococcus haemolyticus* (n = 2), and

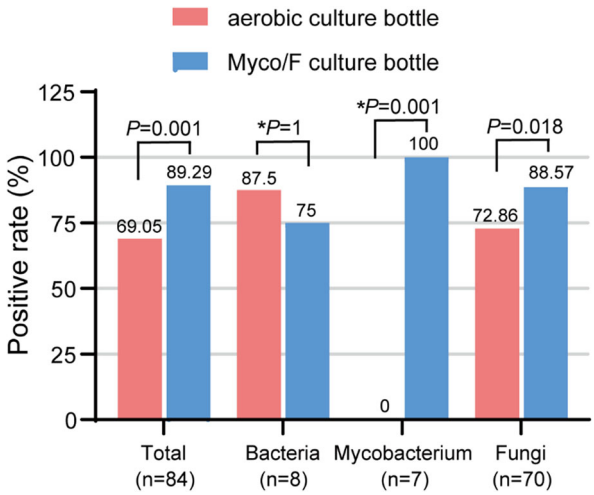

Fig. 1 Comparison of positive rate of aerobic culture bottles and Myco/F bottles at detecting bacteria, *Mycobacterium*, and fungi. (chi-square test, *Fisher's exact test). $P < 0.05$ indicated statistical difference

Corynebacterium tuberculostearicum ($n = 1$) observed (Table 2).

Myco/F Culture Bottle Compared with Aerobic Culture Bottle

In the BSI group, 49 out of 84 cases had positive results in both the aerobic and Myco/F culture bottles, while 9 cases were negative only in the Myco/F culture bottles. The positive rates of aerobic and Myco/F culture bottles were 69.05% and 89.29%, respectively, showing statistically significant differences ($P = 0.001$). Among bacteria cases, five out of eight tested positive in both the aerobic and Myco/F culture bottles, while one case tested positive only in the Myco/F culture bottles. The corresponding positive rates were 87.5% and 75%, respectively. Out of the 70 cases tested, fungi were detected in both culture bottles in 43, while in 19 cases, fungi were only detected in the Myco/F culture bottles. The positive rates observed in these culture bottles were found to be significantly different, with the Myco/F culture bottles displaying significantly lower rates compared with the aerobic culture bottles (72.86% and 88.57%, respectively; $P = 0.018$). Significantly, *Mycobacterium* was exclusively detected in the Myco/F culture bottles (Fig. 1). In addition, as presented in Table 3, the Myco/F culture bottles could identify more *T. marneffei* BSIs ($P = 0.028$).

DISCUSSION

This retrospective study analyzed the results of two types of blood culture bottles utilized for the detection of BSIs in HIV-positive patients. The study revealed that the predominant pathogens causing BSIs in patients with HIV were primarily fungi, particularly *T. marneffei*. Additionally, Myco/F culture bottles exhibited higher positive rate regardless of the type of BSIs. Furthermore, our study revealed that Myco/F culture bottles offered significant advantages in the detection of mycobacteria and fungi.

Currently, blood culture is considered the gold standard for BSI. When there is suspicion of BSI, the guidelines recommend using both aerobic and anaerobic blood culture bottles during a single session in order to enhance the detection rate of pathogens [9]. Guidelines from the Infectious Diseases Society of America and the American Society for Microbiology recommend that 20–30 mL of blood per culture set (one aerobic bottle and on anaerobic bottle) is collected and may require 2–3 sets [10]. Generally, within 1 h after identifying sepsis, two sets

Table 3 Evaluation of different blood culture vials for *T. marneffei* BSIs

Pathogen	Number of isolates with the following result:				
	Positive with aerobic culture bottle only	Positive with Myco/F culture bottle only	Positive with both bottles	*P*-value	χ^2 value
T. marneffei	8	18	37	0.028	4.846

BSI bloodstream infection

of blood samples (aerobic and anaerobic culture) before antibiotic use are collected for culture [11]. We observed a significantly low positivity rate (8 of 246, contain contaminants) in the anaerobic culture bottles, with the same pathogens as the aerobic culture bottles. Hence, they were excluded from the analysis in our study. Although blood culture is the gold standard for the diagnosis of BSI, its limitations affect its clinical application. The sensitivity of conventional blood cultures for the diagnosis of BSIs is suboptimal [12], and its consistency with clinical results is also lower than that of metagenomic next-generation sequencing (mNGS) [13]. According to our research data, the positive rate of the aerobic culture bottles was found to be 69.05%. Low positive rate leads to missed clinical diagnoses, which are associated with high mortality rates in hospitalized patients with HIV-associated BSIs.

BSI is a leading cause of hospitalization among individuals living with HIV. The selection of suitable detection methods can enhance the pathogen detection rate and minimize the risk of missed diagnoses. The Myco/F culture bottles are primarily designed for culturing fungi and mycobacteria[14]. The components in this culture bottle differ from those in the aerobic culture bottles. Certain nutrients, such as hemolysin, can induce cell lysis, thereby facilitating the liberation of intracellular parasitic pathogenic bacteria such as mycobacteria and fungi from the host cells. When comparing the aerobic and Myco/F culture bottles, we observed that the positive rate of the latter was markedly greater than that of the former (89.29% versus 69.05%; $P = 0.001$). The former culture bottles also demonstrated a significant advantage in diagnosing fungemia, with a higher accuracy rate of 88.57% compared with 72.86% ($P = 0.018$). However, the time to positive report was significantly shorter for aerobic culture bottles compared with Myco/F culture bottles (12.43 ± 6.89 days and 5.47 ± 2.14 days, respectively; $P < 0.001$), which was inconsistent with previous studies [15, 16]. This is related to the higher prevalence of *T. marneffei* infections, as well as infections caused by *Candida* spp. [15]. mNGS is a molecular biology-based method for pathogen detection. It offers rapid detection, high sensitivity, and specificity, and has been utilized in the diagnosis of BSIs[17, 18]. Although mNGS has the aforementioned advantages, it remains challenging to implement in most hospitals due to its high cost and the technological demands associated with detection. Hence, the utilization of Myco/F culture bottles serves as a valuable adjunct to aerobic culture bottles in diagnosing BSI in patients with HIV.

A low $CD4^+$ T cell count is considered to be a risk factor for opportunistic infections. Patients with HIV/AIDS and $CD4^+$ T cell counts lower than 200 cells/μl are at a heightened risk of opportunistic infections caused by pathogens such as *T. marneffei*, MTB, and *Cryptococcus neoformans* [19–21]. The incidence of BSIs, the epidemiological distribution of the involved pathogen species, and mortality rates can vary depending on geographical location [2, 6]. Whether HIV infection also affects the type of pathogens that cause BSIs, a study in eastern China [22] found that the pathogens of community-associated bloodstream infections are mainly bacteria. Wenzhou is situated on the southeastern coast of China and is known for its humid climate during the Mei-yu season, which provides favorable conditions for the growth and transmission of *T. marneffei*. Our study demonstrated that *T. marneffei* was responsible for 75% of patients with BSIs, which was significantly higher compared with other pathogens. This finding aligns with the study conducted by Lai et al. [23]. Mycobacterial infection should not be overlooked in individuals with advanced HIV/AIDS. In our study population, seven episodes of mycobacterial BSIs would have been missed if only the aerobic culture bottles had been used. Due to the relatively slow growth of mycobacteria, the automated blood culture system failed to detect pathogen growth before the aerobic culture bottles were discarded. Furthermore, no statistically significant difference was observed in the detection rate of bacteria between the two groups (87.5% versus 75%). Hence, the Myco/F culture bottles are better suited for the detection of fungal and mycobacterial BSIs compared with the conventional culture bottles.

Mixed infections are frequently observed in patients who have advanced HIV/AIDS [1, 17]. Regrettably, our study revealed that only two patients had different pathogens detected in their blood samples, and these pathogens were found in separate culture bottles. We hypothesized the presence of competition among different pathogens in the culture medium, with the identified pathogen exhibiting inhibitory effects on the growth of other pathogens [24]. Another possible reason is that pathogens with relatively slow growth rates may have the potential to go unnoticed.

There are some limitations to our study. First, this is a single-center retrospective analysis. Second, this study utilized blood culture results and clinical diagnosis as the criteria for judgment; clinical diagnosis is mainly based on clinical symptoms and other laboratory results, such as 1,3-beta-D-glucan test, galactomannan test, interferon gamma release assay, and sputum culture, but some patients may have misdiagnosis due to lack of etiological evidence. Third, mixed infections are very common in advanced HIV/AIDS patients, blood cultures often cannot report multiple pathogens simultaneously, and higher bacterial loads are often easily detected, potentially introducing detection bias. In addition, the guideline does not require the number of fungal culture bottles, and this study only used one fungal culture bottle, which may lead to false negatives. Furthermore, this study did not analyze the influence of culture-based anti-infective therapy on patient outcomes, thereby providing additional evidence for the benefits of culture bottles. In future clinical practice, increased attention should be given to BSIs in patients with HIV. Furthermore, it is imperative to include individuals from the non-HIV population to more comprehensively assess the diagnostic efficacy of these two culture bottles in the context of BSIs. It is also necessary to conduct multicenter prospective studies.

CONCLUSIONS

Fungi, particularly *T. marneffei*, are more prevalent in BSIs among HIV-positive individuals in southeastern China. The Myco/F culture bottles exhibit both high sensitivity and specificity in diagnosing BSIs in HIV-seropositive patients, making them an excellent choice for detecting fungal and mycobacterial infections. It is recommended that suspected BSI cases in patients with HIV undergo examinations using both standard culture bottles and Myco/F culture bottles concurrently. This approach is beneficial in enhancing the detection rate and reducing potential mortality among HIV-infected patients.

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Declarations

Conflict of Interest. The authors affirm that they do not have any financial or other conflicts of interest.

Ethical Approval. This study was approved by the ethics committee of Wenzhou Central Hospital (Ethics approval reference number: L2022-01-033). Informed consent from patients was waived due to the retrospective nature of this study.

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